

American Heart Journal

Vol. 32

JULY, 1946

No. 1

Original Communications

FOREIGN BODIES IN AND IN RELATION TO THE THORACIC BLOOD VESSELS AND HEART

III. INDICATIONS FOR THE REMOVAL OF INTRACARDIAC FOREIGN BODIES AND THE BEHAVIOR OF THE HEART DURING MANIPULATION

LIEUTENANT COLONEL DWIGHT E. HARKEN, M.C., AND MAJOR PAUL M. ZOLL, M.C.
ARMY OF THE UNITED STATES

ARISTOTLE wrote, "The heart alone of all viscera cannot withstand serious injury."¹ At the end of the last century, Stephen Paget² had gained no optimism, for he commented, "Surgery of the heart has probably reached the limit set by Nature to all surgery: no new method, and no new discovery, can overcome the natural difficulties that attend a wound of the heart," yet less than one year later, on Sept. 9, 1896, Rehn,³ in Frankfurt, successfully sutured a stab wound of the right ventricle. Within ten years over a hundred such cases of cardiac suture had been reported, and now several hundred more have been added, the majority of which have been successful.

Elective intracardiac surgery first centered around the removal of foreign bodies. Decker⁴ reported that there had been at least twenty-four successful cases by 1939. There will be more when the results of surgery in World War II are known.

The brilliant work and writing on heart surgery by Doyan, Duval, Tuffier, Carrel, Graham, Beck, and Cutler mark the evolution from dreams to experiment and from experiment to bold human adventure.

Today it is fair to expect certain simple intracardiac maneuvers to be successful. The door has been opened by modern anesthesia and the technique of rapid blood replacement.

The purpose of this paper is twofold: first, *to elaborate on the indications for surgical removal of intracardiac foreign bodies*; and second, *to describe and*

Appreciation is expressed to the Sias Laboratories of the Brooks Hospital, Brookline, Mass., for their assistance in the publication of this article and for the provision of facilities for further investigation in cardiac surgery now being undertaken.

Presented as the substance of the Joseph Strickland Goodall Memorial Lecture at the Society of Apothecaries, London, on June 26, 1945.

Received for publication Sept. 21, 1945.

illustrate the behavior of the heart during manipulation. The discussion is based on experience in the removal of missiles distributed as indicated in Table I, and is concerned principally with the 26 pericardial and 13 intracardiac missiles. Fig. 1 shows the intracardiac missiles that have been removed. There are seven from the chamber of the right ventricle, four from the chamber of the right auricle, one from the left auricular cavity, and one from a small cystic myocardial hernia in the left ventricle.

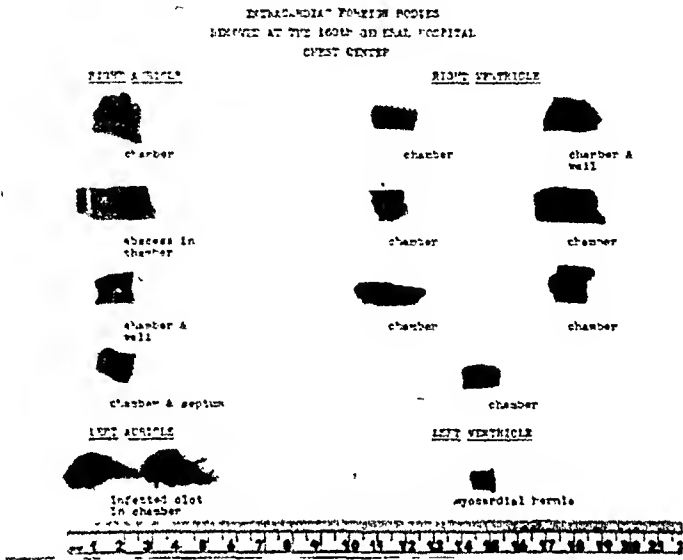


Fig. 1.—Intracardiac foreign bodies that have been removed.

TABLE I. DISTRIBUTION OF 134 MISSILES IN RELATION TO THE PERICARDIUM, HEART, AND GREAT VESSELS

Pericardial	26
Involving pericardium but principally pulmonary	17
Intracardiac	13
On great vessels (and in walls)	35
Intravascular (three embolic)	7
On great vessels but principally pulmonary	17
Mediastinal but not directly on great vessels	19
Total	134
Deaths	0

INDICATIONS FOR REMOVAL OF INTRACARDIAC FOREIGN BODIES

The first part of this discussion pertains to the indications for the removal of intracardiac foreign bodies.

The pressure of work during the past year has been such that there was little time for review of the medical literature. When such consultation was sought it was usually disappointing. Often it has been difficult to accept reported foreign bodies as "in the heart" when there has been no confirmation of the location by autopsy or surgical exploration. Even surgical exploration may be uncertain in the presence of an infected hematoma within the pericardium or auricle. In short, it is probable that some of the reported "intracardiac" missiles were not in the heart.

Personal experience confirmed the difficulty of accurate localization of metallic fragments in relation to the heart. Almost one-half of the foreign bodies referred to us as "in the heart" were found by careful fluoroscopic examination to lie outside it. Furthermore, one-third of the cases that we thought earlier in our work might represent intracardiac fragments were found at operation to be extracardiac.

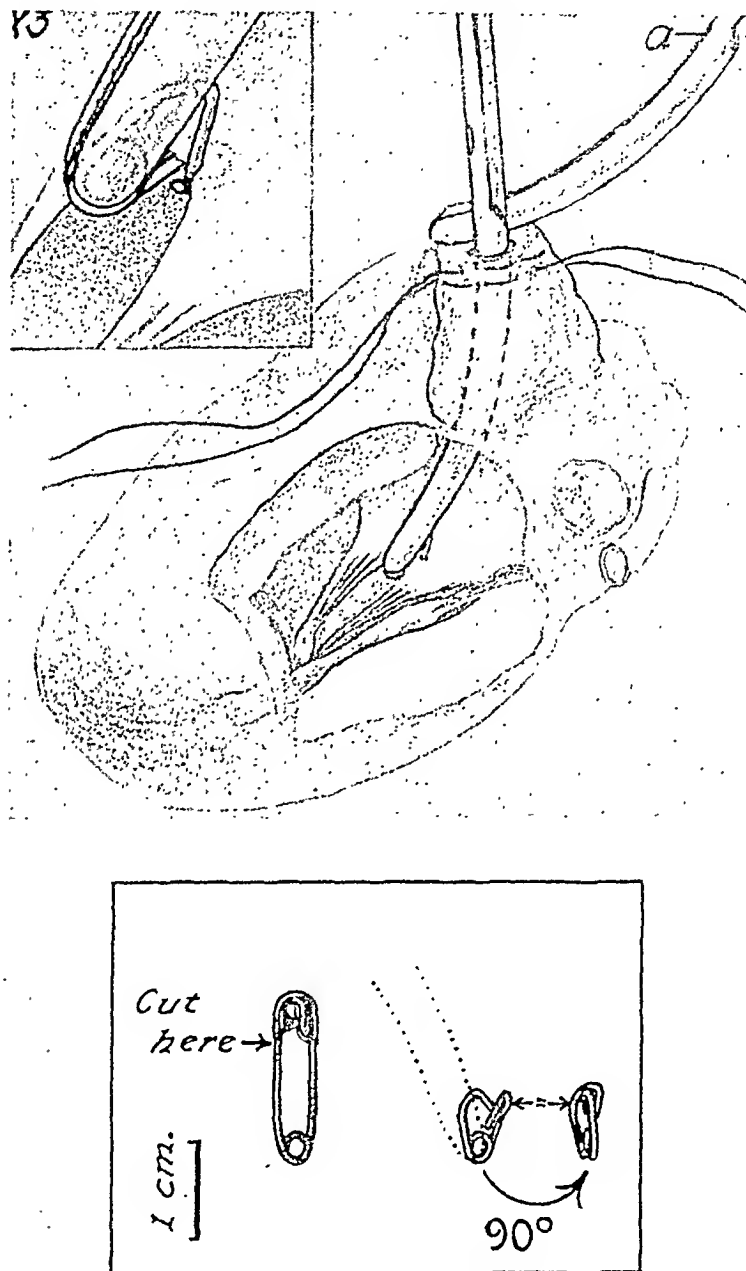


Fig. 2.—Method of implantation of a foreign body in the heart of a dog.

Such confusion makes it very difficult to assess the risks to health and life of intracardiac missiles. During the past year, however, these problems arose, and it was necessary to establish a working policy. This policy was formulated from information borrowed from the medical literature, from our own hypothetical concepts, and from a limited amount of previous experimental work on animals.

It was felt that certain cardiac foreign bodies should be removed, for the following reasons: (1) to prevent embolus of the foreign body or associated thrombus, (2) to reduce the danger of bacterial endocarditis, (3) to prevent recurrent pericardial effusions, and (4) to diminish the incidence of myocardial damage.

For these reasons it was decided to remove half of the missiles presumed to be in the heart that came under our observation. Applicability of these factors was determined, in part, by the size and location of the foreign body and by clinical manifestations. Clinical evidence supporting these tenets has accumulated during the year.

The first and most obvious indication for removal is the *prevention of embolus of the foreign body or of an associated thrombus*. Several instances of this accident have been recorded in the literature and two additional cases may be briefly noted here.



Fig. 3.—Typical endocarditis surrounding the implanted foreign body.

One of our patients developed, shortly after injury, a hemiplegia coming from a thrombus in the left auricle. The foreign body lay in the interauricular septum and right auricle. It was removed from the right auricle.⁵

A second and particularly significant case has recently been described by Lieutenant Colonel Nichol.⁶ In this instance the missile was in the left ventricle. Embolism causing hemiplegia occurred over two weeks after injury.

The second tenet, that certain foreign bodies should be removed *to reduce the danger of bacterial endocarditis*, was based in part on experimental work with dogs.⁷ Foreign bodies were placed in various locations in the heart, and bacterial endocarditis developed spontaneously. Fig. 2 shows the manner of

implantation and the type of foreign body used. Figs. 3 and 4 illustrate typical resultant bacterial valvulitis and septic embolic infarcts. It was feared that foreign bodies might behave in the same way in human hearts.



Fig. 4.—Typical septic embolic infarcts of experimental bacterial endocarditis.

Our clinical support for this indication is not complete. One patient ran a course suggesting subacute bacterial endocarditis with spiking fever, tachycardia, and an acute episode of right upper quadrant pain with jaundice. Response to surgical removal of the missile and its associated thrombus from the right auricle was immediate and dramatic, with prompt recovery from an almost moribund state. Furthermore, in bacteriologic studies of four intra-auricular foreign bodies, pathogenic organisms grew from three of these foreign bodies. One of these lay in a small abscess in the center of a mural thrombus in the right auricle. Similar studies in five right intraventricular fragments showed growth of bacteria in only one instance; here also the foreign body lay in an abscess within a mural thrombus in the chamber of the right ventricle. No bacteriologic studies are available on the four other cases.

It cannot be said that these infected niduses represent true bacterial endocarditis nor that they would have produced it. Nevertheless, these findings have encouraged us to remove the missiles.

The third reason for the removal of missiles is to *prevent recurrent pericardial effusions*. This point has been stressed in the medical literature. We have seen two such cases, but the symptoms were not severe enough nor were the fragments of sufficient size to justify intervention. Size and clinical manifestations will inevitably govern surgical removal of cardiac missiles. Fig 1 shows those that we have removed. We have elected to leave more than we have removed; the former were, of course, both small and silent.

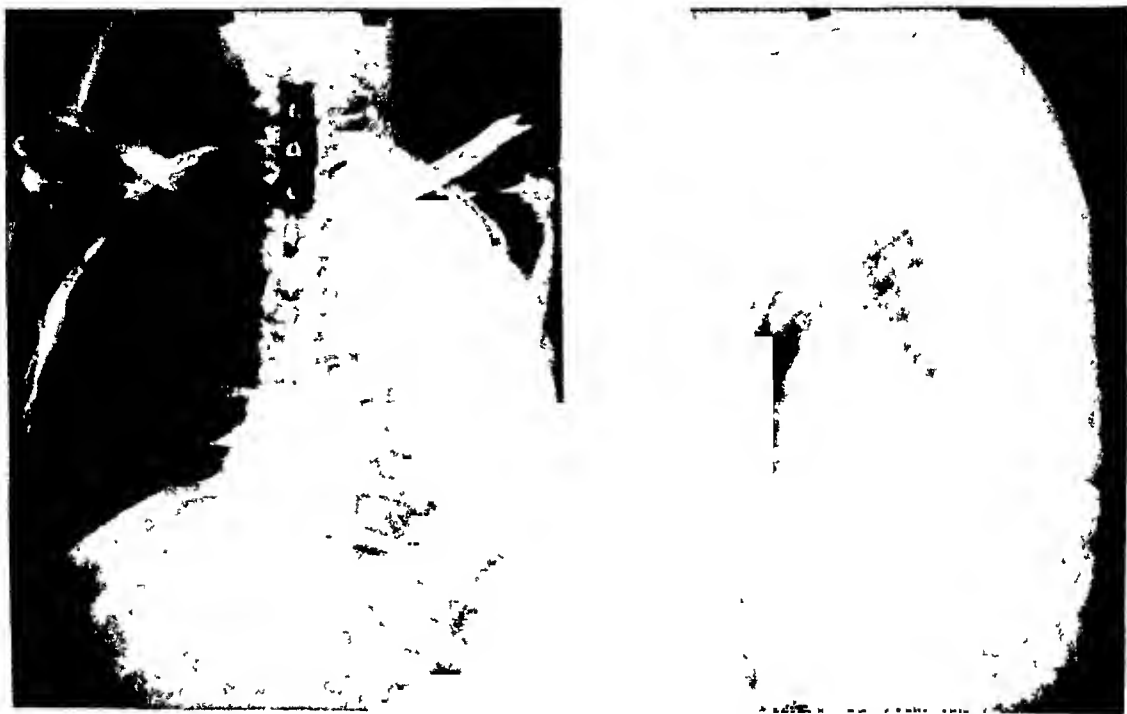


Fig. 5.—Posteroanterior and lateral roentgenograms demonstrating the original position of the fragment in the right ventricle.

Finally, cardiac missiles should be removed to *diminish the incidence of myocardial damage*.

Damage of the right ventricular wall overlying the site of a migratory missile has been noted in one instance. This case is presented in some detail, for it is of special significance in several respects. In particular it demonstrates clearly that a foreign body, simply lying in the chamber of the heart, can produce considerable damage of the overlying myocardium in three months. This case further indicates that operative removal per se need not cause significant myocardial injury.

LeR. R., a 29-year-old infantry sergeant was struck by a mortar shell fragment in the right lower posterior aspect of his chest on July 21, 1944, near St. Lo, France. Fluoroscopy and roentgenograms (Fig. 5) showed a metallic foreign body pulsating with the heart, lying in the anterior portion

of the right ventricle, just to the left of the midline. An electrocardiogram on July 25 (Fig. 6) showed only inverted T waves in the right-sided precordial leads CF_1 , CF_2 , and CF_3 . By August 8 the T wave in CF_3 had become upright, so that the tracing appeared normal.

At operation on August 15, the missile was grasped through an incision in the right ventricle, only to be pulled from the forceps by the wriggling myocardium and to be lost from sight and palpation, in the blood stream. The technical details of cardiomy have been presented elsewhere.⁵

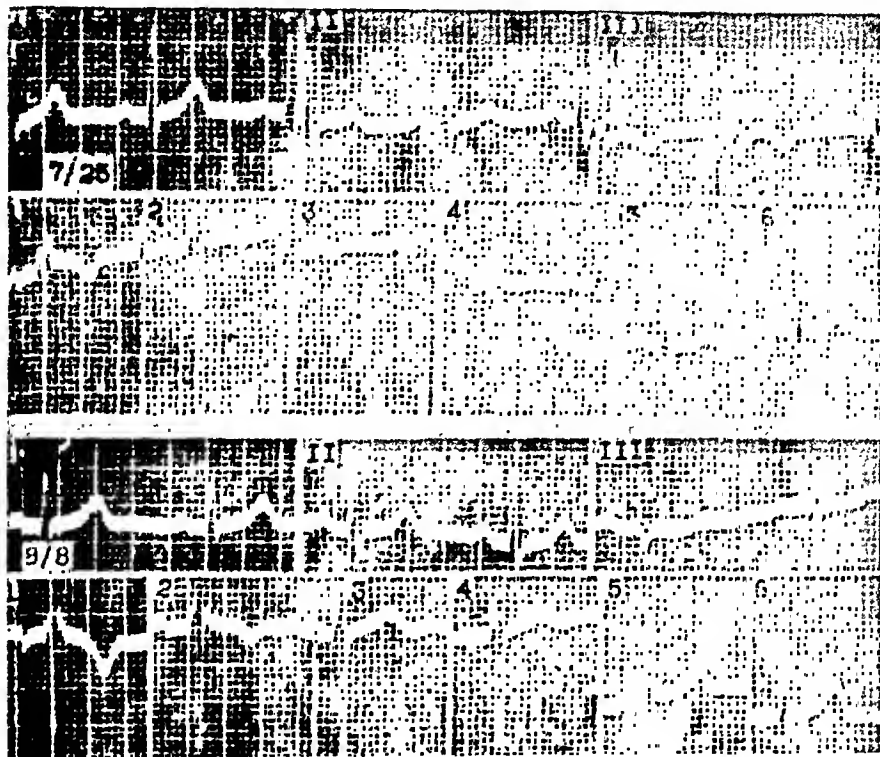


Fig. 6.—Electrocardiograms before the first cardiomy. The figures in the upper left corner of each segment indicate the leads (Roman numerals for the limb leads and Arabic numerals for the precordial leads CF_1 to CF_6). The date of tracing appears in lower margin of the section.

After operation, the foreign body was found by roentgenograms (Fig. 7) to be in the right auricle over the opening of the inferior vena cava. On August 17 the electrocardiogram (Fig. 8) showed elevated S-T segments in Leads I and II, which fell by September 1. Later the T waves also became sharply inverted in Leads I and II and in the left-sided precordial leads CF_4 , CF_5 , and CF_6 . This pattern suggests acute anterior wall myocardial damage and may be related to the incision made in the right ventricle near the septum in the anterior surface of the heart, or to the associated pericarditis.

At a second cardiomy on Nov. 16, 1944 (three months later), the missile was visualized and palpated in the right auricle just above the entrance of the inferior vena cava. It escaped again, however, and fell back into the right ventricle to the position seen in the postoperative roentgenogram (Fig 9). A significant point is demonstrated by these roentgenograms; that the imperfect lateral position gives the impression that the missile is in the chest wall. Electrocardiograms (Fig. 10) showed no specific acute change following this second

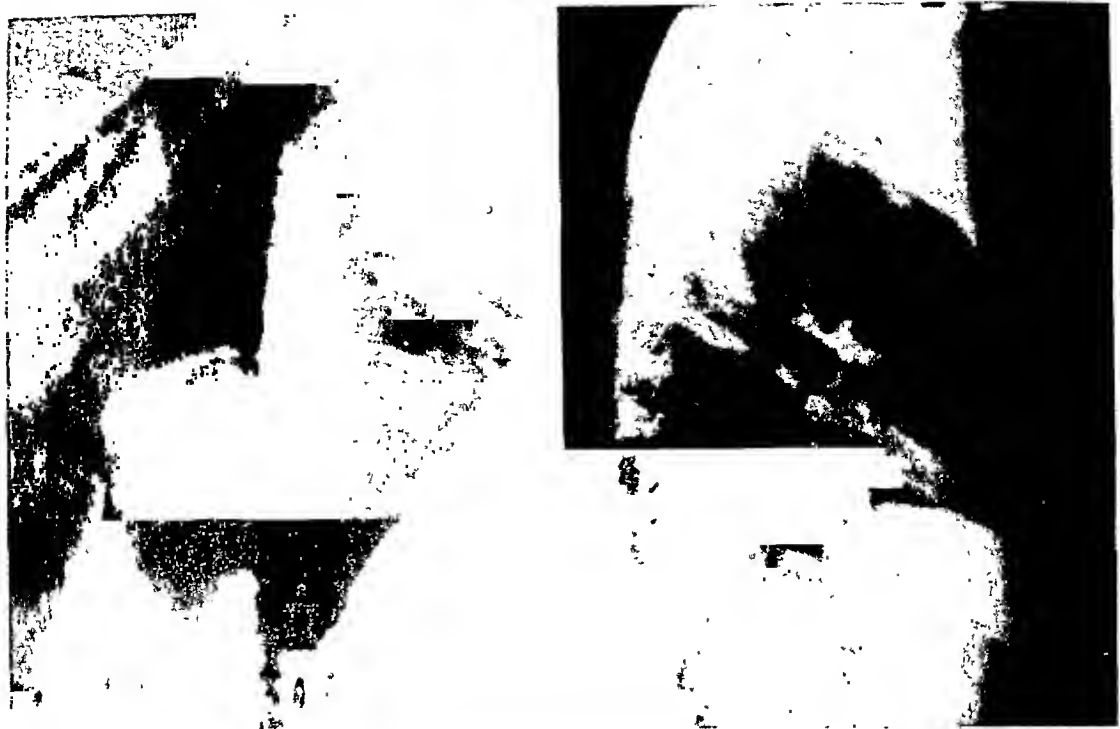


Fig. 7.—Posteroanterior and lateral roentgenograms showing the position of the fragment in the right auricle after the first cardiectomy.

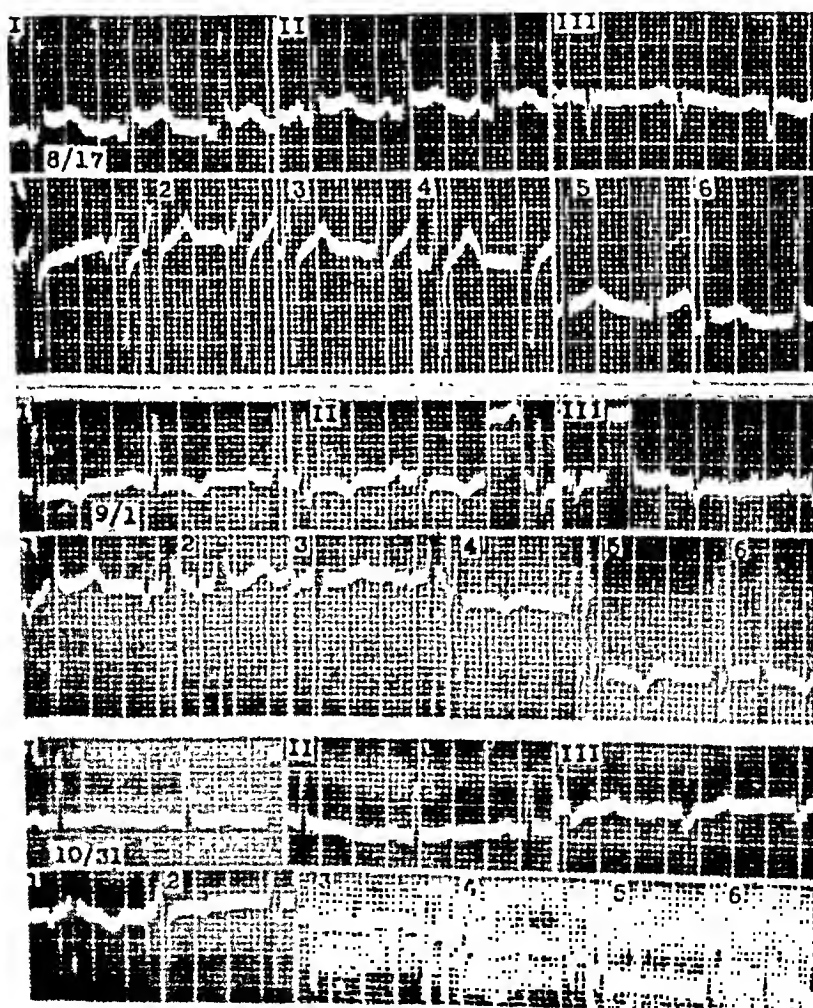


Fig. 8.—Electrocardiograms taken after the first cardiectomy.

cardiotomy, but only a progressive return toward normal of the T waves in Leads I, II, CF₅, and CF₆.

On Feb. 19, 1945, a third cardiotomy was performed, again through an anterior approach similar to the first operation. The old scar of the first incision in the right ventricle was found to be solidly healed after this interval of six months. Considerable fibrous pericarditis had developed but it did not limit cardiac motion nor obstruct blood flow. Near the apex of the right ventricle,

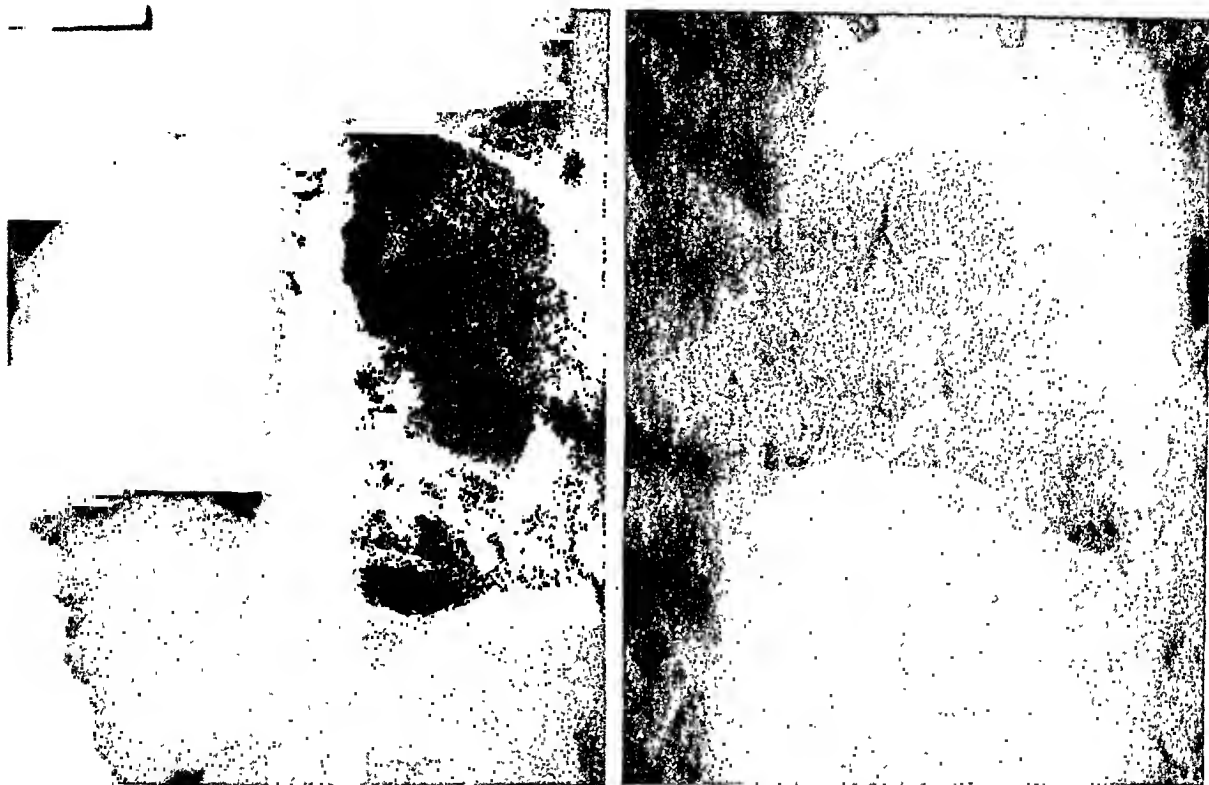


Fig. 9.—Posteroanterior and lateral roentgenograms of the fragment again in the right ventricle after the second unsuccessful cardiotomy.

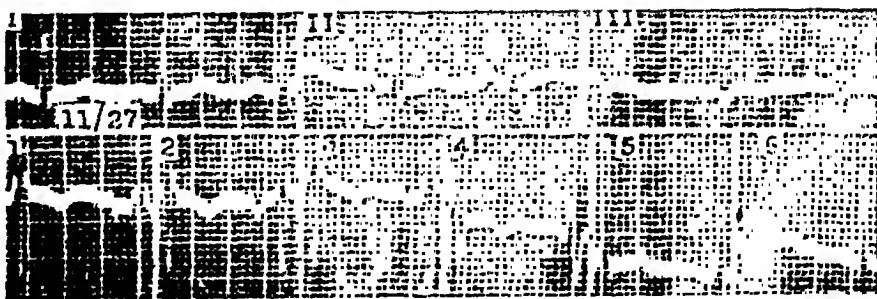


Fig. 10.—Electrocardiogram taken after the second cardiotomy.

however, the muscle wall was thin, flabby, and discolored; the foreign body was palpable in the underlying right ventricular cavity. This area of myocardial damage had been produced by the muscle wall rubbing over the fragment during the three months following the second operation. The heart was opened again through this flabby area, and the shell fragment (Fig. 1) was grasped by forceps and removed with only moderate difficulty (Plate I). The period of

intracardiac manipulation extended for approximately three minutes, in three episodes. Showers of extrasystoles were noted during the process of removal. The cardiac behavior at this time is recorded in the electrocardiograms (Fig. 11) that are discussed later.

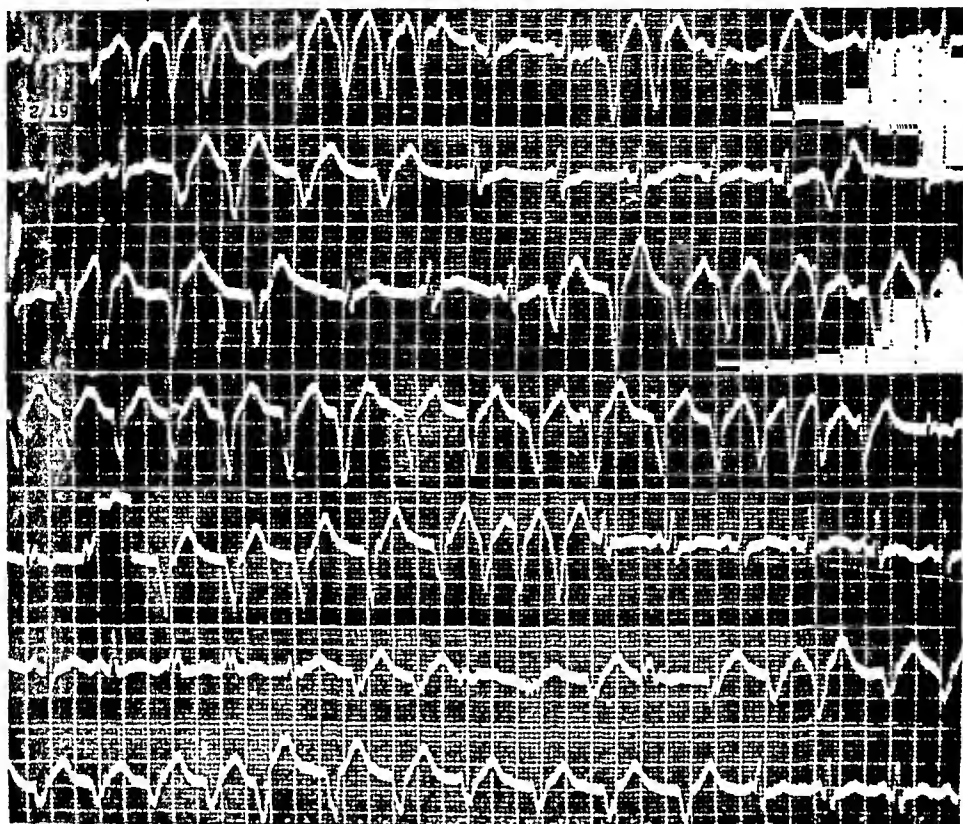


Fig. 11.—Electrocardiographic tracings taken during the successful cardiomy at the time of removal of the fragment from the right ventricle.

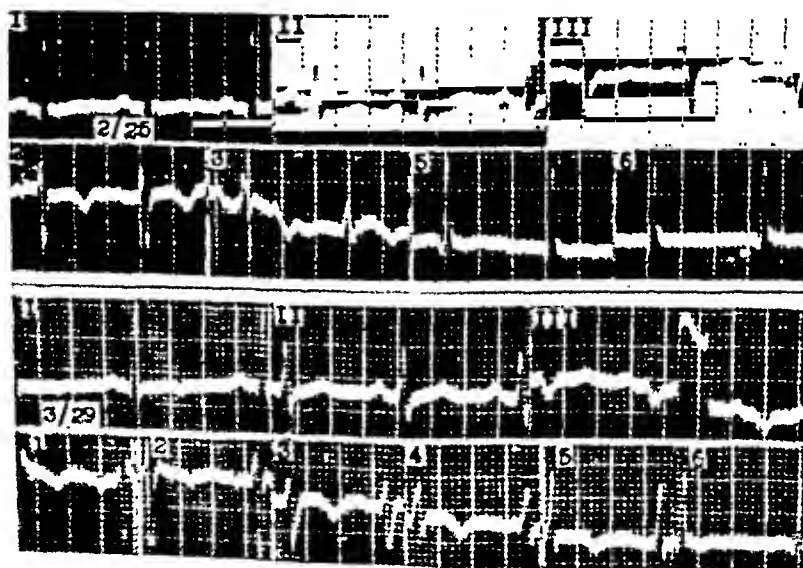


Fig. 12.—Electrocardiograms following the third cardiomy.

Convalescence following operation was uneventful. Postoperative electrocardiograms (Fig. 12) showed only left axis deviation and low or inverted T waves in Lead I and the precordial leads, findings which were consistent with pericardial reaction and residual minor damage in the mid-precordial area.

Fig. 13 recapitulates the migration of the missile from the right ventricle to the right auricle and back again. Fig. 14 shows the patient clinically well at the time of discharge.

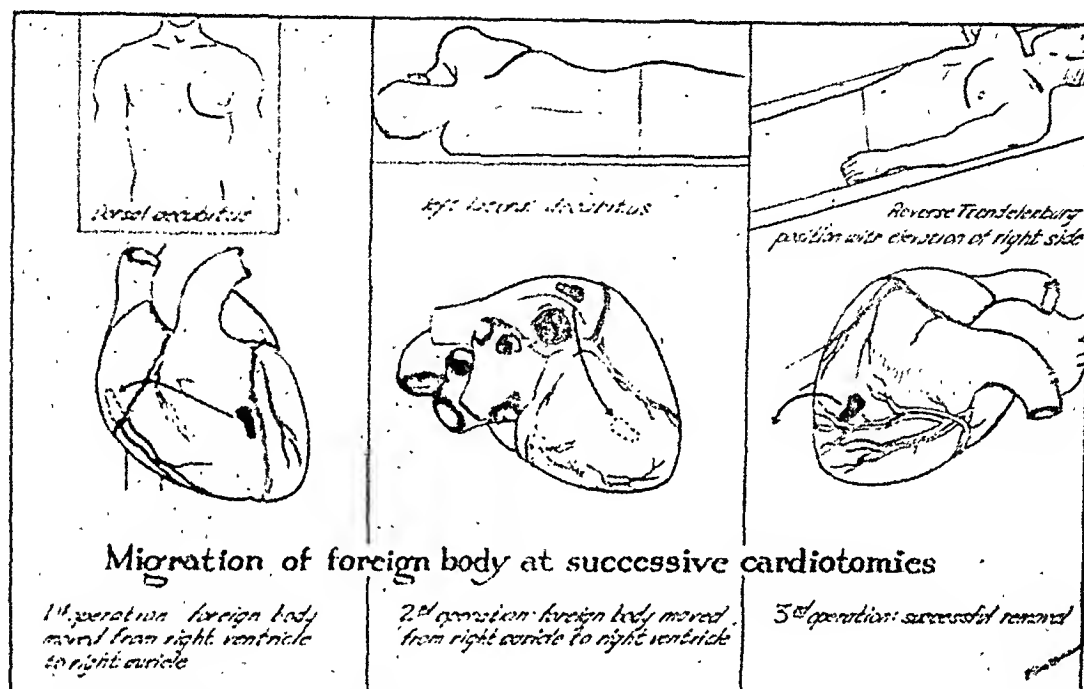


Fig. 13.—Diagrammatic presentation of the patient's position at operations and of the migration of the missile.

In the only case in this series of a foreign body in the left ventricle, the missile lay in a small cystic myocardial hernia (Fig. 15). Roentgenkymographic studies showed diminished amplitude of pulsation at the apex and passive left ventricular dilatation during systole, suggesting early ventricular aneurysm or hernia. Electrocardiograms (Fig. 16) showed a persistent pattern characteristic of extensive damage of the anterior wall of the left ventricle. The changes consisted of low voltage, deep Q_1 , absent R_1 and inverted T_1 , together with inverted and "W-shaped" QRS complexes and sharply inverted and peaked T waves in the left-sided precordial leads.

At operation, the foreign body was found in the left ventricle, in a cystic zone of myocardial damage 1.5 cm. in diameter. It was ballotable in the defect in the cardiac wall, and paradoxical pulsation of this area of the ventricle was noted. The missile (Fig. 1) was removed without hemorrhage because of a mural thrombus. The thrombus was not disturbed. The myocardial defect was closed and reinforced with two superimposed pericardial grafts. It is interesting that electrocardiographic tracings taken frequently during the operation showed no evidence of cardiac irritability at any time, except for a few ventricular extrasystoles during the process of endotracheal intubation.

Direct observation at operation indicated that the danger of rupture of this myocardial hernia was real and was aggravated by the presence of the foreign body. It is thought that this operation in which the missile was removed and the defect was repaired prevented progression of the myocardial damage and possible rupture of the heart.



Fig. 14.—Patient LeR. R. at the time of discharge.

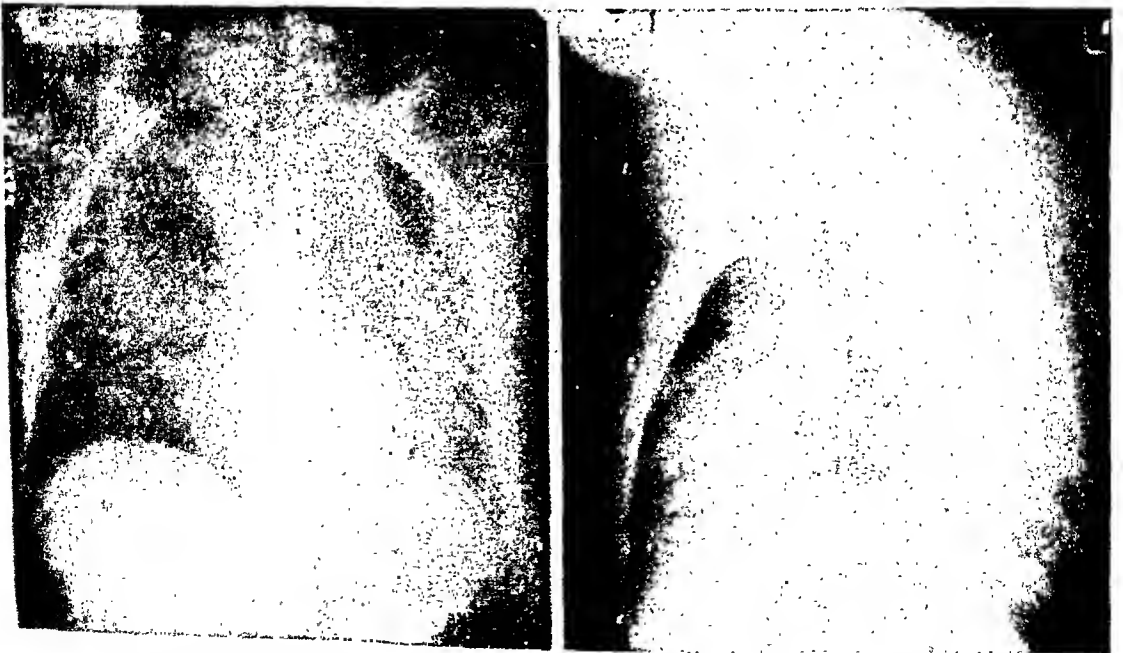


Fig. 15.—Posteroanterior and lateral roentgenograms of a missile in the left ventricle.

A third patient was seen by Major Fred Jarvis.⁸ In this case, the wall of the right ventricle overlying a migratory missile degenerated and death ensued.

A fourth case, this from our own series, seems particularly significant in that it demonstrates in combination several of the tenets under discussion.

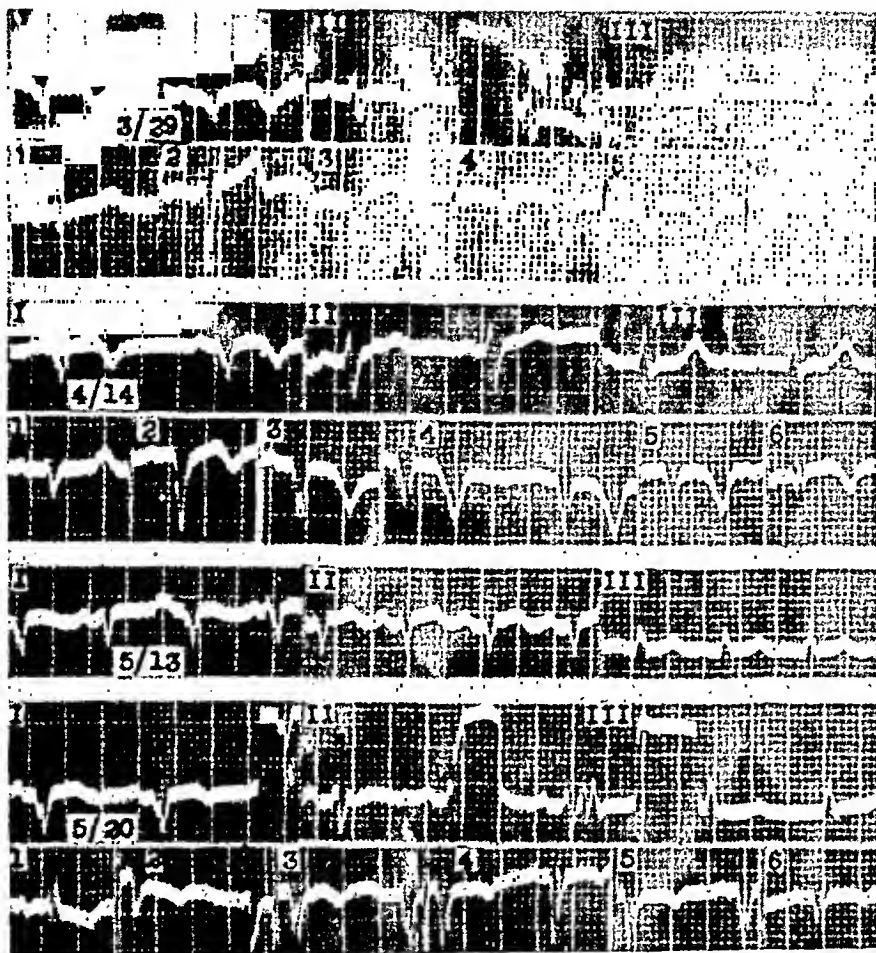


Fig. 16.—Electrocardiograms showing left ventricular damage.

This soldier developed an empyema (hemolytic *Staphylococcus aureus* and *Clostridium welchii*) following injury by a shell fragment in the left anterior aspect of the chest. The empyema was treated by decortication and, later, by open drainage before he arrived at the 160th General Hospital Chest Center. Three massive and two minor episodes of hemorrhage occurred in the six months following injury; there were also bouts of pyrexia reaching 103° F. that did not appear to be due to the empyema. Fig. 17 shows the size and location of the foreign body, and Fig. 18 presents typical electrocardiographic tracings. Before operation there were right axis deviation with low R₁ and deep S₁, low diphasic T₁, and upright pointed T₂ and T₃. The precordial leads were normal. These findings did not help in localization of the missile.

At operation on May 18, 1945, the empyema was found to communicate with a laceration in the pericardium and underlying adherent left auricle. There was a laceration of the auricle that was plugged by a large infected intracardiac hematoma. The 2 by 1 by 1 cm. missile was wrapped in cloth and lay

in this clot. The fragment was removed from the left auricle together with the clot and the infected clot. *Cl. welchii* and *Escherichia coli* were grown on direct culture of the foreign body. The surgical exposure, location of the pericardial laceration, and type of repair are described elsewhere.⁵



Fig. 17.—Posteroanterior and lateral roentgenograms of a fragment in the left auricle. Radio-opaque oil is seen in the empyema pocket.

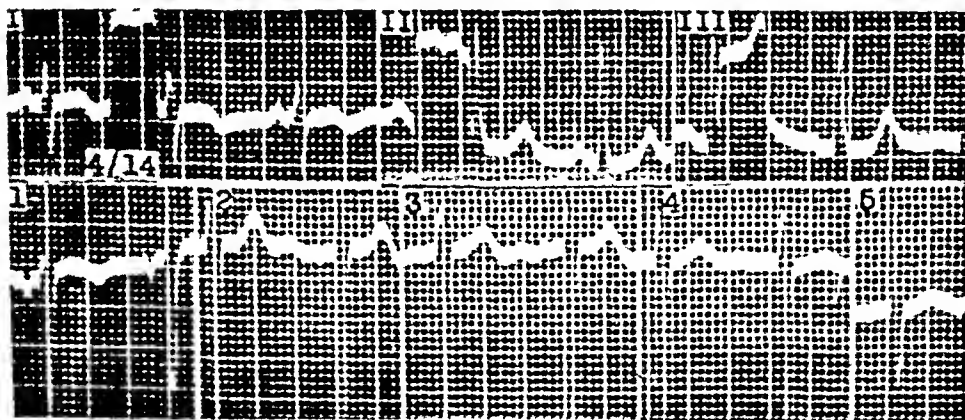


Fig. 18.—Electrocardiograms before operation in the patient with left auricular laceration and an intra-auricular shell fragment.

After operation there was rapid improvement of the empyema, and no further episodes of hemorrhage or pyrexia occurred. Electrocardiograms (Fig. 19) show deep and sharp inversion of T_1 and inverted T waves in CF_5 , but no other significant change. This case appeared to embrace most of the indications for removal of an intracardiac foreign body: extensive thrombus with potential embolus, gross intracardiac contamination and infection, pericardial involvement, and damaged myocardium with repeated hemorrhage.

Two additional factors may assume importance in the decision to remove intraeardiae foreign bodies: namely, *pain and cardiac neurosis*.

Pain has been associated with some of the pericardial missiles but with only one of the intraeardiae group. This was in a man in whom the missile had migrated from the auricle to the ventricle. A similar case is described by Lieutenant Colonel Miscall.⁹

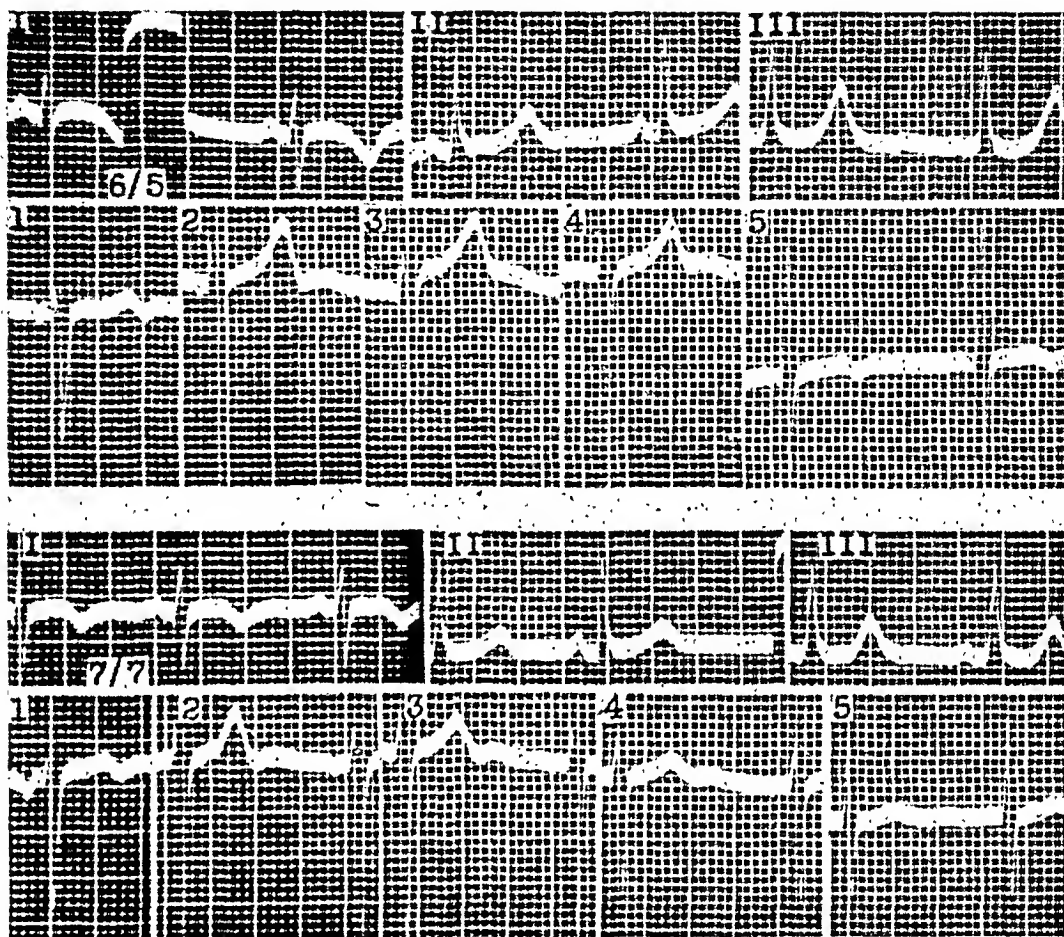


Fig. 19.—Electrocardiograms following left auricular cardiectomy.

Cardiac neurosis may become an important consideration in spite of every effort to reassure the patient. All our patients with foreign bodies in or near their hearts have wanted them removed. Professor Grey Turner has said: "In addition to the characteristic cardiac symptoms just mentioned, there may be neurotic manifestations which mainly depend on the attitude of the patient to the knowledge that he harbors a foreign body in one of the citadels of his wellbeing."¹⁰

These are fragments of clinical evidence directing the surgeon to remove the larger or symptomatic missiles. The experience has been brief, yet convincing to us. It is emphasized that we decided to leave fifteen fragments in the heart. These, of course, were small and silent. Surgery was undertaken in four additional cases where intraeardiae fragments were present. Two of these fragments were deemed too hazardous to remove at exploratory *pericardiectomy*, and two were not recovered at *cardiectomy*.

The cost of operation to the patients has not been great; none died; all have done well and apparently have normally functioning hearts now. Final conclusions cannot be drawn for several years.

BEHAVIOR OF THE HEART DURING MANIPULATION

The technique used in approaching and removing cardiac and mediastinal foreign bodies cannot be discussed here. During this experience, however, some elementary rules of surgical conduct governing exposure and manipulation of the heart have become clear. Some salient features of cardiac exposure are the following:

1. *Adequate direct exposure of the involved region.* This requires the use of a variety of approaches.

2. *The conservation of the skeleton of the thoracic cage.* Bone and cartilage may be divided but not removed. After operation there should be neither deformity nor defect.

3. *Minimal dislocation of heart from the position of optimal function.*

4. *Maintenance of moist epicardium in the exposed heart.* One per cent novocaine solution has been used; it may have additional advantages in reducing cardiac irritability.

It is with the third principle of exposure that the remainder of this discussion is to deal; namely, maneuvers that are not tolerated well by the heart during intracardiac and pericardial surgery. One case of an extracardiac and one case of an intracardiac operation will be used as illustrations.

The first demonstrates the effect of dislocation of the heart from the position of optimal function during the removal of an extracardiac foreign body that lay in a pericardial abscess well back on the diaphragmatic surface. The location of the pericardial missile can be seen in the roentgenograms in Fig. 20. At operation the foreign body was found on the posterior phrenic surface of the heart in a pericardial abscess containing about 18 c.c. of pus. To gain access to this area the heart had to be lifted out of the pericardial sac (Plate II). Because this procedure caused fall in blood pressure and circulatory failure, the heart had to be replaced frequently for rest and return of blood pressure toward normal after relatively short periods of dislocation. Many irregularities in rhythm that were apparently extrasystoles occurred. Also, a marked cardiac dilatation, particularly of the right ventricle, developed, with the result that the heart became too large for the pericardial sac (Plate III).

Electrocardiographic tracings taken during operation (Fig. 21) showed variations in rhythm consisting of ventricular extrasystoles (at 300), wandering pacemaker (varying P-R interval at 302 and 307), and A-V nodal rhythm (at 313, 315, and 316). It was at the time that the nodal rhythm occurred that a particularly prolonged and alarming episode of circulatory failure developed during a period of dislocation of the heart; after recovery, normal sinoauricular tachycardia returned (at 317, 319, and 332) (Fig. 21).

An additional change in the electrocardiogram was also related to dislocation of the heart. At 257 the S wave became broad and notched and the QRS

Plate II.



Plate III.



Plate I.—Colored photograph at the instant of incision into the right ventricle. This is the third cardiomy in Fig. 13.

Plate II.—Colored photograph illustrating the maneuver of dislocation of the heart from the pericardial sac.

Plate III.—Colored photograph showing marked right ventricular dilatation following dislocation of the heart. Plates II and III were taken during the operation recorded in the electrocardiographic tracings in Fig. 21.



Plate I.

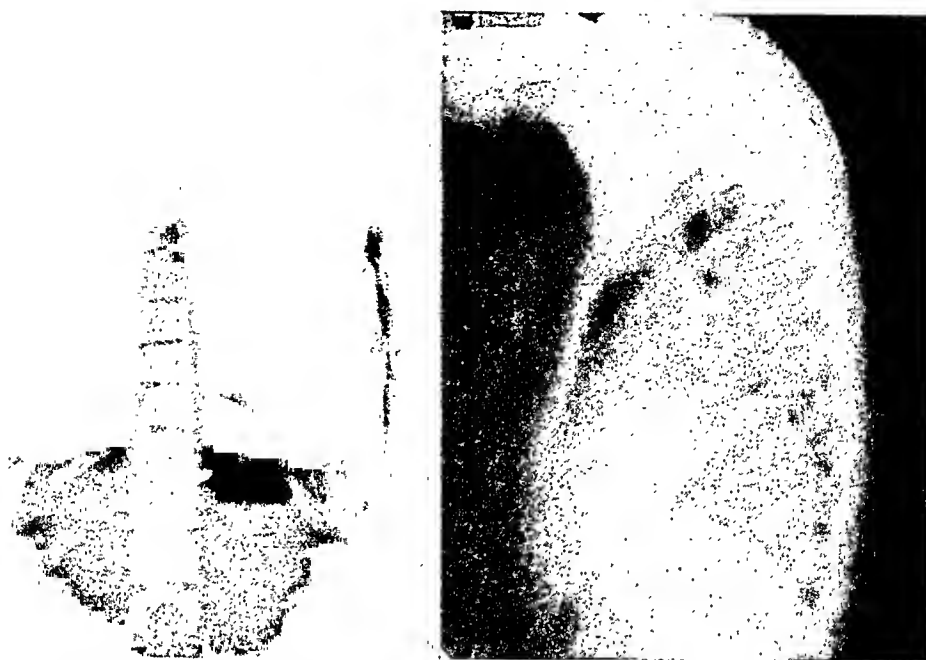


Fig. 20.—Posteroanterior and lateral roentgenograms showing a foreign body in a pericardial abscess.

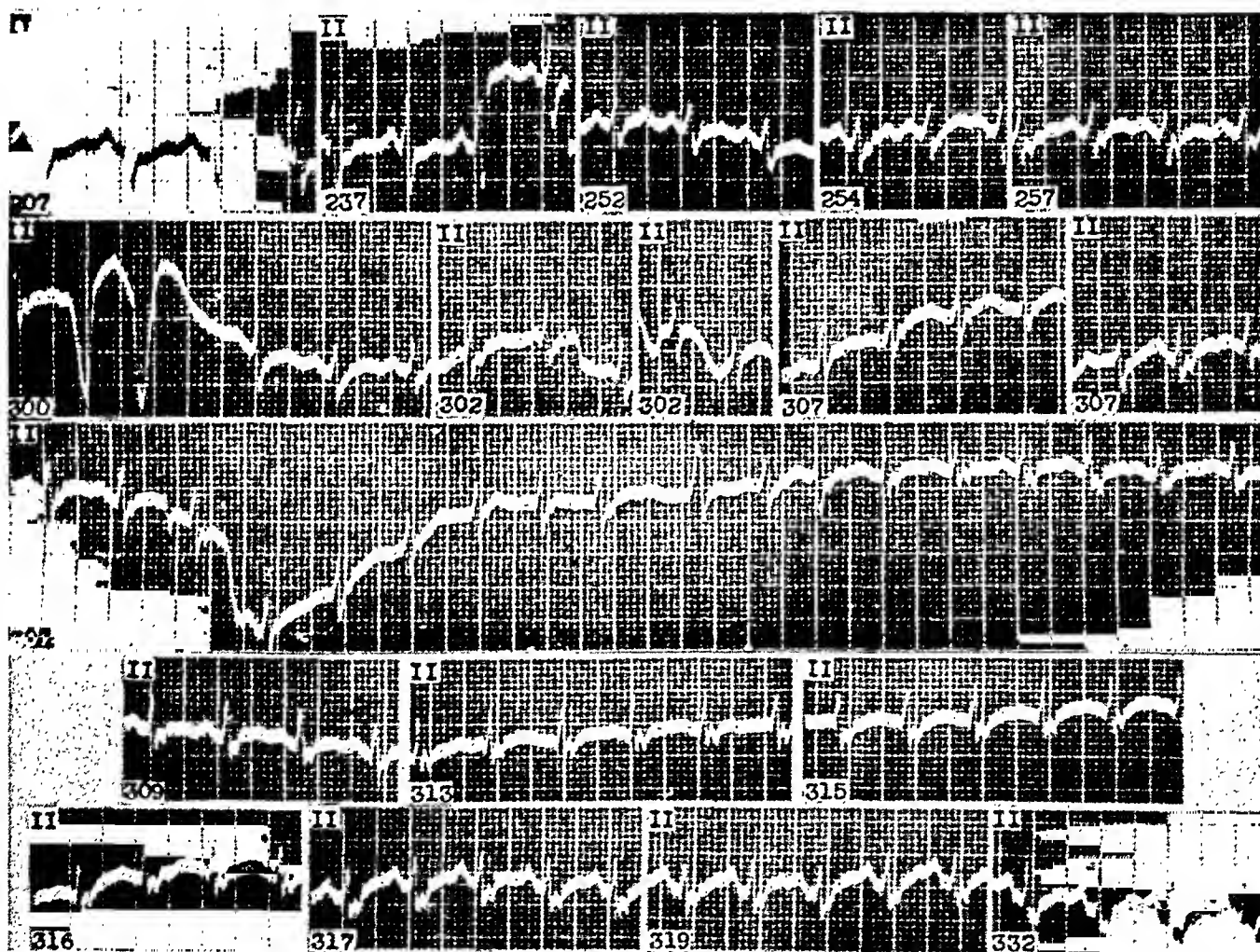


Fig. 21.—Electrocardiograms taken during the operation for removal of the pericardial foreign body. The number in the lower corner of each segment indicates the time (o'clock) the tracing was taken.

interval lengthened to 0.13 second, in contrast with the normal complexes which were present at 207 and 237 before cardiac manipulation. It is unfortunate that this abnormality was recorded in Lead II only, but it may be regarded as indicating, at least, intraventricular block or bundle branch block, probably of the *right* side. The abnormal QRS complexes persisted throughout the operation, but the complexes had returned to normal four days later. This delay in conduction was found, by direct visual inspection, to be correlated with dilatation of the right ventricle, certainly an unusual observation in the human subject. It may be considered, in part at least, a result of the increased time necessary for the conduction of the impulse through the greatly dilated right ventricle.

The intolerance of the heart to dislocation was demonstrated in this case in two ways: first, by the ventricular dilatation, with incomplete bundle branch block, and second, by varying types of arrhythmia and circulatory collapse. Dislocation of the heart may produce torsion of the great vessels and obstruction to outflow of blood, with fall in blood pressure resulting from the diminished cardiac output, and with ventricular dilatation from the increased resistance to blood flow.

This type of experience has led us to avoid the apical suture as a means of exposing inaccessible areas of the heart. Generally speaking, in elective cardiac surgery, the approach can be so planned that precise and comfortable exposure is provided for any part of the heart. The various techniques for approaching different cardiac areas and chambers have received consideration and illustration elsewhere.⁵

Experience has also demonstrated that the classical hemostatic cardiac grips, which are intended to provide a bloodless field, are badly tolerated. These maneuvers upset cardiovascular dynamics and should therefore be used only as means of last resort.

The intolerance of the heart to obstructed blood flow is in sharp contrast to its stability during other cardiac and intracardiac procedures. The surface of the heart was manipulated, sutures were taken in the muscle, and actual incisions were made into the chambers of the heart with little disturbance. It was felt that keeping the surface of the heart moist with warm saline or novocaine solution was important in reducing the degree of irritability. There were minor evidences of irritability, such as extrasystoles, wandering pacemaker (varying P-R interval), and even A-V nodal rhythm. Usually these phenomena were not accompanied by any significant clinical manifestations. Such minor abnormalities were often produced by noncardiac procedures during anesthesia and operation. They were often evoked by endotracheal intubation, spreading of the ribs, and manipulations of the hilar and mediastinal structures.

More extensive manipulations inside the cardiac chambers by the exploring finger or forceps to remove intracardiac thrombus or foreign body were less well tolerated, though frequently no abnormalities were noted. Marked cardiac irregularity in the form of multiple ventricular extrasystoles was commonly seen. The patient with the three cardiomyotomies, already discussed, demonstrated

this particularly well. Fig. 11 shows the electrocardiogram obtained as the foreign body was grasped and extracted from the right ventricle. There were showers of ventricular extrasystoles from varying foci in both ventricles, producing runs of ventricular tachycardia up to sixteen seconds in duration. Direct observation of the irregular heart action and examination of the electrocardiogram did raise the fear of impending ventricular fibrillation. At the end of the procedure, however, upon the removal of the irritating forceps and missile from the ventricular chamber, the ventricular tachycardia ceased promptly and the P-R interval returned to normal in three beats. In our experience so far, these irregularities have been relatively benign.

SUMMARY

Evidence is presented in support of the following indications for the removal of some intracardiac foreign bodies: (1) to prevent embolus of the foreign body or associated thrombus, (2) to reduce the danger of bacterial endocarditis, (3) to prevent recurrent pericardial effusions, and (4) to diminish the incidence of myocardial damage. The additional factors of pain and cardiac neurosis are also considered.

The behavior of the heart during various types of manipulation is described. Dislocation of the heart from the position of optimal function is poorly tolerated, as are other procedures which upset cardiovascular dynamics by obstruction to blood flow.

REFERENCES

1. Aristotle: *De Partibus Animalium*, Lib. III, Cap. 4.
2. Paget, S.: *The Surgery of the Chest*, Bristol, 1896, John Wright & Co., p. 121.
3. Rehn, L.: *Verhandl. d. Gesellsch. d. Naturforscher und Aerzte*, 1896.
4. Decker, H. R.: Foreign Bodies in the Heart and Pericardium—Should They Be Removed? *J. Thoracic Surg.* 9: 62-79, 1939.
5. Harken, Dwight E.: Foreign Bodies in and in Relation to the Thoracic Blood Vessels and Heart. I. General Considerations and Technique of Removing Foreign Bodies From the Chambers of the Heart, *Surg., Gynec. & Obst.* (To be published.)
6. Nichol, Arthur D.: Personal communication.
7. Harken, Dwight E.: Experiments in Intracardiac Surgery. I. Bacterial Endocarditis, *J. Thoracic Surg.* 11: 656-670, 1942.
8. Jarvis, Frederick: Personal communication by Paul C. Samson.
9. Miscall, Laurence: Personal communication.
10. Turner, G. Grey: Foreign Bodies in the Heart Twenty-three Years, *Surgery* 9: 832-852, 1942.
11. Harken, Dwight E., and Williams, Ashbel C.: Foreign Bodies in and in Relation to the Thoracic Blood Vessels and Heart. II. Migratory Missiles, *Am. J. Surg.* (To be published.)

EXPERIENCES WITH DICUMAROL (3,3'-METHYLENE-BIS-[4-HYDROXYCOUMARIN]) IN THE TREATMENT OF CORONARY THROMBOSIS WITH MYOCARDIAL INFARCTION

PRELIMINARY REPORT

IRVING S. WRIGHT, M.D.
NEW YORK, N. Y.

FOLLOWING the discovery, isolation, and synthesis of dicumarol the anti-coagulant properties of this and allied substances were demonstrated in animals by Link and his co-workers¹ and by Bingham, Meyer, and Pohle.² Immediately, several groups of clinical investigators initiated studies to determine the effectiveness of this substance in the prevention and treatment of thrombophlebitis with and without pulmonary or other embolic phenomena.³⁻⁶ The technique for its use and the remarkable success achieved are now a matter of established record.

Early in our studies at the Vascular Clinic of the New York Post-Graduate Medical School of Columbia University, we considered the possibility of the use of this therapeutic agent in the treatment of coronary thrombosis. It is extremely difficult to evaluate its effectiveness in a particular patient who has suffered from an uncomplicated attack of coronary thrombosis in its early stages since we are, at present, unable to predict with certainty which patient will have a rapid series of secondary episodes of thrombosis, which one will have one or more embolic phenomena, and which patient will prove to have an uneventful recovery from the immediate attack. It is recognized that the patient who has a series of episodes of thrombosis in different radicals of the coronary tree within a short period of time or whose original thrombus propagates, extending centrally and thus blocking off additional branches of the same coronary artery, has an increasingly serious prognosis with each episode or extension. Experience has clearly demonstrated that once a person has more than two episodes of thrombosis within a period of three to four weeks there is a strong likelihood that further episodes will follow and that the prognosis is poor. The author has personally cared for many patients through such a course, helpless to prevent repeated attacks of thrombosis and death. In the same manner, once a patient has developed a mural thrombus and has had one or more embolic phenomena, the prognosis is grave indeed: especially if the mural thrombus is in the right heart thus producing pulmonary emboli.

Presented before the California Heart Association, Stanford University, San Francisco, Calif., Oct. 18, 1945.

Received for publication Jan. 21, 1946.

The first patients in this group to receive dicumarol were selected because:

1. They had suffered repeated episodes of multiple thrombi in different areas of the coronary tree or the original thrombus had propagated. The clinical evidence for these criteria consisted of repeated attacks characteristic of the coronary syndrome with precordial pain, fever, leucocytosis, and increased sedimentation rate, with confirmatory electrocardiographic findings.

2. They had suffered repeated embolic phenomena either pulmonary or to other areas. (It was recognized that certain of the pulmonary emboli might have arisen in the extra cardiac circulation, but following myocardial infarctions the percentage of pulmonary emboli is a considerable one and, from whatever source, repeated pulmonary emboli have an increasingly serious prognosis.)

3. They had evidence suggesting that both Factor 1 and Factor 2 were active.

Unfortunately, previously compiled adequate statistical data regarding the prognosis of each of these special categories in patients not treated by anti-coagulants are unavailable. This fact combined with the difficulty of running a properly controlled series for each of the suitable subdivisions has mitigated against the drawing of final conclusions regarding the value of dicumarol in the treatment of coronary thrombosis.

The first patient in this series was treated with dicumarol in May, 1942. Since then, 76 patients with acute or recurrent coronary thrombosis have been treated with dicumarol by the author or under his direction.⁷ These have been in both civilian and Army hospitals. Forty-three of these were selected because they qualified under one of the aforementioned categories as having a serious prognosis. Twenty-eight had evidence of multiple thrombi or propagation, 12 had multiple embolic phenomena, and three showed evidence of both types of episodes.

The experience with these groups encouraged us to increase the series by using this substance in 33 patients suffering from uncomplicated first or second attacks of coronary thrombosis.

In addition to dicumarol, all patients received conventional treatment including rest, opiates, barbiturates, aminophylline, and oxygen according to the indications.

A total of 15 patients died: 11 from the series of 43 with the more serious prognosis and four from the series of uncomplicated cases. Only four of the deaths occurred as a direct immediate result of the insult of the thrombosis. Three of these were in the complicated group and only one was in the uncomplicated group. Eleven deaths occurred as a result of cardiac failure two or more weeks after their last acute episode. Of these, eight were in the complicated group and three were in the uncomplicated group. Eight autopsies were performed. No evidence of hemorrhage or any other effects of dicumarol, which could have produced death, were found. The livers from three patients showed slight fatty infiltration which was not considered to be of serious degree. Of the

43 patients in the complicated group, 38 ceased having evidence of extension, additional thrombi, or embolic phenomena after the dicumarol therapy was inaugurated.

Sixty-one patients recovered from the attack during which this study was carried out. While the over-all mortality figures do not differ markedly from the anticipated rate for single attacks of coronary thrombosis, certain facts should be considered in this regard.

1. Forty-three of these patients were selected because they had complications known to be associated with a very high mortality. (As mentioned previously, exact figures are not available but 60 to 70 per cent mortality would approximate the anticipated risk of this group of patients in the experience of the author.) Only 11 (25 per cent) of these patients died in the episode for which they were treated.

2. Of the 33 patients having their first or second uncomplicated attack at the time of onset of treatment with dicumarol, four died (12 per cent) against an anticipated death rate of 20 to 30 per cent.

The observation of individual cases seemed more suggestive. Abstracts of several case histories of particular interest are therefore included.

CASE HISTORIES

CASE 39.—A 50-year-old man was admitted to the hospital complaining of severe precordial pain of four hours' duration which radiated down the left arm. He had suffered from one previous recognized attack of coronary thrombosis nine months before. The first attack had been diagnosed on the basis of precordial pain with prostration, fever, increased sedimentation rate, leucocytosis, and electrocardiographic tracings typical of an anterior myocardial infarction. The patient was hospitalized for ten weeks and made an uneventful recovery; he had only the single moderately severe episode. He was able to return to administrative work and, aside from easy fatigability, had no marked untoward effects.

The second attack, during which the patient was hospitalized, was accompanied by more severe pain and breathlessness. The second day the oral temperature reached 101° F. The sedimentation rate rose until on the seventh day it reached 62 mm. per hour. The white count increased to 12,400 with 78 per cent polymorphonuclear cells. The electrocardiogram which was normal on admission showed changes on the third day typical of an acute anterior infarction as follows: there was a convex S-T segment with late inversion of the T waves in Lead I, a concave S-T segment in Lead III, and an absent Q wave with an upright T wave in Lead IV. Serial tracings showed changes which tended to revert toward normal by the tenth day. On treatment with rest, morphine, and whiskey he did well. By the twelfth day the patient was comfortable, the fever had subsided, and the sedimentation rate was down to 28 mm. per hour. He appeared to be on the way toward an uneventful recovery when suddenly he was seized with an agonizing precordial pain and once more developed fever which reached 103° F. This time the course was much more stormy. He required oxygen therapy for his dyspnea and cyanosis, his liver edge extended down 2 fingerbreadths below the costal margin and was tender, and the sedimentation rate increased to 70 mm. per hour. The white cell count rose to 16,000 with 80 per cent polymorphonuclear cells. The electrocardiogram showed marked changes again, but this time they were typical of a posterior myocardial infarction with some residual changes from the anterior infarction as follows: T₁ was isoelectric and there was a concave S-T interval with a high origin in Lead II, a deep T₂, and absence of R₁ with deep T₄. The rhythm was regular.

A third episode occurred seven days later and his precordial distress became more constant. He was dyspneic and cyanotic and was kept in an oxygen tent constantly. The electrocardiogram showed further disturbance suggestive of posterior wall damage.

Dicumarol was started immediately after the third attack in the hope of decreasing the tendency toward further thromboses. It was administered according to the technique outlined later in this paper. The prothrombin time was kept as closely as possible between 30 and 35 seconds for thirty days. The patient's course was uncertain for one month but he gradually improved and after three and one-half months he was having only moderate discomfort and was able to leave the hospital. There were no evidences of the formation of additional thromboses nor of propagation of former thromboses after the inauguration of dicumarol therapy.

As noted earlier in this report no one can say with certainty whether or not dicumarol influenced the course of this patient by tipping the balance away from a tendency toward thrombosis. Nevertheless, this type of history was repeated sufficiently often in this series to warrant giving serious consideration to the possibility of such an action.

CASE 42.—A 36-year-old man was admitted to a hospital complaining of precordial pain of moderate severity and without radiation. He had suffered from the anginal syndrome produced by effort for two months prior to the present acute episode. He had an oral temperature of 100° F. on admission. The second day this rose to 101.5° F. and then slowly subsided. On rest with morphine, the pain disappeared within thirty hours. The sedimentation rate reached a peak of 36 mm. per hour on the fifth day and the white count reached 11,400 with 76 per cent polymorphonuclear cells. The electrocardiogram showed typical changes of a posterior (T₂ type) myocardial infarction on the second day with a tendency toward reversion to normal by the seventh day. His course was mild. By the sixth day he felt so well that it was difficult to keep him in bed. On the ninth day he had a sudden sharp pain in the right posterior chest associated with some difficulty in breathing comfortably. The next day he coughed up bright red stained sputum. A pleural friction rub was readily heard over the right lung base posteriorly on normal breathing. No evidence of peripheral thrombophlebitis could be found on physical examination. X-ray films showed a shadow characteristic of a small pulmonary infarction in the right lower lobe laterally.

Four days later there was a recurrence of acute pain in the right lung base posteriorly and again bright red blood was raised by coughing. Two days after the second episode a third one occurred, this time in the left lung base.

It was believed that the patient had developed a mural thrombus in the right heart, following his myocardial infarction, from which segments of fresh thrombus were breaking off to become pulmonary emboli. The possibility of an undetectable thrombus existing in an extra cardiac vein was also considered as a source of the pulmonary emboli.

Regardless of which source was correct, anticoagulant therapy appeared logical and dicumarol was given according to the technique set forth elsewhere in this paper. It was continued for one month.

During the first two weeks a prothrombin time of approximately 30 to 35 seconds was maintained. During the second two weeks this was gradually allowed to revert toward normal. No further pulmonary emboli occurred after the dicumarol therapy was started.

While it is recognized that minute pulmonary emboli may occur which cannot be diagnosed during life, we can safely state that none of clinical significance occurred following the use of dicumarol. Again we cannot prove beyond a doubt that dicumarol affected the course of this syndrome, but the possibility is certainly worthy of consideration.

CASE 18.—A 47-year-old man was admitted to the hospital Nov. 26, 1942, complaining of increasing dyspnea on exertion. He gave a history of hypertension which was first recog-

nized in 1934. Between 1934 and 1942 the systolic blood pressure had varied between 160 and 200 mm. of mercury. He did not know the diastolic pressures. The patient had no symptoms. One brother and two sisters had hypertension. In August, 1942, the patient observed that he became dyspneic after walking only three blocks. This was fairly constant. One evening (exact date uncertain) in September, 1942, about 8:00 P.M., while lying in bed, he suddenly became very dyspneic. He began to wheeze and at the same time developed pain in the lower substernal area which radiated to the shoulder. This attack lasted fifteen minutes and then completely disappeared without medication. A blood pressure reading taken shortly afterward showed the usual elevation. There was no history of previous attacks of breathlessness or of any form of allergy.

On physical examination on admission, the patient did not appear ill. The blood pressure averaged 200/150. He had an emphysematous type chest that was hyperresonant to percussion. There were no râles in the chest. The fundi showed copper-wire arteries. All peripheral pulses were strong. The heart was enlarged to the left and downward. The apex beat was felt just lateral to the mid-clavicular line in the sixth intercostal space. At times a triple thrust was felt in the apex region. There was a booming first sound at the apex and an accentuated aortic second sound. No murmurs could be heard. There was occasionally a gallop rhythm at the apex accompanied by pulsus alternans. No friction rub was heard.

Blood counts, serology, and urine analysis were normal. The highest sedimentation rate was 30 mm. per hour. X-ray films of the chest indicated left ventricular enlargement and some pulmonary congestion. The first electrocardiogram revealed left ventricular preponderance and evidence of myocardial damage compatible with a previous anterior myocardial infarction (T_1 type).

The day after admission the patient became dyspneic. The liver was enlarged to about 4 cm. below the costal margin. The neck veins became engorged and moist râles were heard in the chest. Mereupurin was given; diuresis ensued, the râles disappeared, and the liver became smaller. It was necessary to give mereupurin about every five days in order to keep the urine output approximately equal to the intake. On the fourteenth day after admission the patient developed epigastric pain, wheezing, and went into mild collapse. The pulse became rapid and thready and the blood pressure dropped to 140/90. A low-grade fever was noted. Electrocardiographic studies showed evidence of a superimposed anterior infarct (T_1 type with coving). A pericardial rub developed at the apex. At this time a left ventricular aneurysm was suspected on the basis of x-ray findings. Because of the prognosis and the possibility of propagation of the original thrombus, the development of new thrombi, and the development or extension of mural thrombi we decided to use dicumarol. It was administered according to a somewhat lower schedule of dosage than outlined elsewhere in this paper, the prothrombin time being kept between 26 and 30 seconds. A total of 1,500 mg. of dicumarol was given. No evidences of hemorrhage were ever noted.

On the twenty-first day the patient went into mild peripheral failure and pulmonary edema. Digitalis was then cautiously administered. On the thirty-first day ventricular extrasystoles developed. Quinidine was given to prevent ventricular fibrillation. On the thirty-second hospital day the patient slumped forward in bed and died suddenly.

The significant autopsy findings were as follows: The pleural, pericardial, and peritoneal cavities were free from excessive fluid. The lungs were slightly heavy and more reddish brown than usual. No infarctions were noted. On section the alveolar walls were thickened in some areas and ruptured in others. The heart weighed 570 grams. It presented the configuration of the essential hypertensive heart with hypertrophy of the left ventricle. At the apex there was a small aneurysm of the left ventricle which measured 3.5 cm. in diameter. It projected out about 1.5 cm. beyond the surrounding heart tissue. The left coronary artery was tortuous and contained numerous calcific plaques. Just beyond the origin of the left coronary artery the lumen was obliterated by dense, grayish-white tissue apparently representing an old organized thrombus. The area of occlusion measured 1.8 cm. in length. Five centimeters beyond the distal extremity of this thrombus another occlusion was

present. It measured 0.5 cm. in length and consisted of reddish-gray, somewhat stratified, tissue. The right coronary artery showed only slight atherosclerosis. Section through the heart revealed the middle part of the major portion of the left ventricular myocardium to consist of yellowish, necrotic, fattylike tissue. The area of necrosis measured 4 to 7 mm. in width. The subepicardial and subendocardial myocardium adjacent to the infarct appeared grossly normal. The wall of the aneurysm measures 3 mm. in thickness. Two of the intertrabecular recesses of the aneurysmal portion of the left ventricle contained dry, granular, reddish-gray masses representing a small mural thrombus. The outer surface of this mural thrombus appeared to be well sealed off by fibrin. The myocardium of the interventricular septum showed extensive areas of scarring. The left ventricular myocardium measured 14 mm. in thickness. The right ventricular myocardium measured 3.5 millimeters. The valves were competent and of tissue paper thickness, and the circumferential measurements were within normal limits. Histologic sections showed all gradations between frank necrosis and early degenerative changes in the left ventricular myocardium. A section of the mural thrombus indicated that it was relatively recent consisting of irregular anastomosing homogeneous acidophilic laminae with the spaces between containing fibrin, red blood cells, and leucocytes. Five sections of the left coronary artery were studied. In all five sections, the intima was markedly thickened by a connective tissue matrix containing calcific deposits, clefts having the configuration of cholesterol ester crystals, and scattered lymphocytes. In several other sections the lumen was either completely obliterated or reduced to small slitlike apertures. In one section the lumen was occupied by an organized thrombus and was partially recanalized. In other sections the vessel contained a relatively recent ante-mortem thrombus.

The determination of the effect of dicumarol in this case is difficult, if indeed any can be demonstrated. The dosage was small and the prothrombin time was kept lower than was the case with later patients. This case does illustrate clearly the complicated picture which is not infrequently encountered. We found evidence of one large and multiple small occlusions, at least some of which may well have occurred at the time of the acute episode of September, 1942. A major recent occlusion was found in the more distal portion of the left coronary artery. This probably occurred with the acute episode of Nov. 12 to 13, 1942. There was evidence of acute myocardial infarction, a ventricular aneurysm, and, of particular interest in this instance, a small mural thrombus in the aneurysm. If this thrombus increased in size, it was perfectly capable of liberating emboli. It was, however, sealed over and no embolic phenomena were discovered. Whether dicumarol played a part in preventing emboli in this case we cannot say. Its use would seem indicated. As in Case 21 dicumarol could have no effect on the course of the condition once the myocardium was sufficiently severely damaged.

CASE 21.—A 42-year-old man was admitted to the hospital complaining of "tearing" substernal pain which radiated into the neck. He developed a fever of 103° F. on the second day. His sedimentation rate rose to 46 mm. per hour and the highest white count (fourth day) was 12,400 with 77 per cent polymorphonuclear cells. The electrocardiogram showed the pattern of anterior myocardial infarction (T₁ type). On routine treatment he improved for six days. Suddenly, while eating, he was seized with a severe pain in the right lateral chest which persisted for two days. The second day he coughed up bright red blood. No friction rub could be heard, but an x-ray film showed a shadow compatible with a pulmonary infarction in the right lower lung field. His heart then developed auricular fibrillation and began to show evidence of decompensation. The following day he had a second similar pulmonary episode in the left base and two days later one in the right middle lung field.

Dicumarol was started on the ninth day and administered according to the technique outlined in this paper. No further recognizable embolic phenomena occurred after dicumarol therapy was instituted. The patient, however, pursued a progressively downhill course and became more severely decompensated. He became orthopneic, moist râles were heard first over both lower lobes, later throughout both lungs. His liver became enlarged and tender, and dependent edema appeared. Oxygen therapy, aminophylline, mercurial diuretics, and digitalis were used without favorably affecting the course of the patient.

He expired thirty days after the onset of his attack and twenty-one days after dicumarol therapy was instituted. The prothrombin time had fluctuated rather widely during the disturbance in fluid equilibrium occasioned by the decompensation, ranging from 23 to 52 seconds, but at no time was there evidence of any hemorrhagic manifestations other than a small purpuric spot on the left thigh and some minor hemorrhagic areas at the sites of venipuncture in both arms. These were such as might be seen in the absence of dicumarol therapy.

Autopsy revealed the following significant findings: The lungs showed typical signs of congestive heart failure. In addition there were evidences of one large, old infarct in each lower lobe and of numerous scattered small infarcts. It was believed after examination that probably none had occurred within a period of two weeks before death. The liver weighed 1,345 grams and showed some evidence of passive congestion with cloudy swelling. The heart weighed 530 grams. Both coronary arteries were tortuous and contained numerous calcific plaques. Five centimeters from the origin of the right coronary artery the lumen was obliterated by a thrombus which was reddish-gray and stratified. It extended about 2 cm. and blocked off several branches of the artery. Sections from this area showed the myocardium of the right ventricle to consist of necrotic, yellowish, fattylike tissue. Microscopic studies showed typical findings of a recent massive myocardial infarction. Attached to the endocardial lining of the right ventricle was an olive-shaped, shiny, mural thrombus 1.5 by 3 cm. in size. On section it appeared to be relatively recent in origin but was completely sealed off by a layer of material resembling fibrin. Other evidence of possible sources of the pulmonary emboli, either intra- or extracardiac, could not be found. Several old occlusions of minute branches of the left coronary artery were found.

While we cannot say with certainty that dicumarol prevented the further propagation of the mural thrombus with a resulting cessation of pulmonary emboli, the following points are in favor of this possibility:

1. The episodes of pulmonary embolism ceased following the inauguration of dicumarol therapy. This was confirmed clinically and pathologically.

2. The mural thrombus, while recent in origin, was sealed off to a remarkable degree.

3. No other sources of pulmonary emboli were found. (The possibility of emboli coming from some obscure venous source was not completely ruled out.)

On the other hand, as anticipated, the use of dicumarol did not affect the course of the process once a massive infarct had occurred. The patient progressed into a condition of cardiac insufficiency and death.

DISCUSSION

It has been observed by numerous workers, and confirmed by the author, that when a thrombosis occurs either in a vein or an artery in one portion of the body it is common, either simultaneously or within a short time, for multiple thrombi to form in other parts of the vascular tree as well as for local propagation of the primary thrombus to take place. The exact mechanism which causes

this phenomenon has never been adequately explained. Perhaps the explanation is the simple one of decrease in the rate of blood flow which occurs secondary to placing the patient at complete bed rest, the most common procedure. Evidence against this hypothesis is found in the work of Baumgarten,⁸ Dietrich,⁹ and others who have demonstrated that blood does not coagulate in a vein that has been ligated carefully at both ends. We have found the clotting time and prothrombin levels to be within normal limits in patients whom we have checked during such episodes.*

The question of the relation of the platelets to this occurrence is worthy of comment. Hueck¹⁰ and von Seemen¹¹ have reported a decrease in platelets during the first three to five postoperative days followed by a marked increase in number. Similar observations have been made in the presence of inflammation^{11, 12} and malignant growths.^{10, 13, 14} The agglutination tendency of the platelets is considered to be increased when the globulin fraction and the fibrinogen increase and the albumin fraction diminishes; in other words, when a shift occurs toward coarse dispersion in the relation between the protein components of the blood.¹⁵ Such shifts tend to take place after operations and accidental trauma and in the presence of infections and malignant growths.

Starlinger and Sametnik¹⁶ have reported that as the shift toward the more coarsely dispersed globulins occurs the normal electrical charge of the platelets, which is negative and hence repellent to the similarly negative proteins, diminishes. This decreases the tendency to repulsion and hence increases the tendency to agglutination.

Stuber and Lang¹² have proposed an explanation for the diminished electrical charge of the platelets. Their explanation is that a retarded circulation results in increasing the carbon dioxide in the blood. This increases glycolysis, which entails a decrease in the negative electrical charge of the thrombocytes with an accompanying increased tendency to agglutination of the thrombocytes.

The action of thrombokinase released from cells as a result of surgery, inflammation, or malignancy might weigh the balance in favor of coagulation and is worthy of further careful study. Numerous other factors have been discussed in this regard. For a review of this subject the reader is referred to the comprehensive monograph by Bruzelius.¹⁷

Multiple thrombosis is an extremely common occurrence in patients with thrombophlebitis; it probably occurs in the majority of patients. Here again available figures are of little significance since autopsy findings have revealed that many thrombi may be present in various venous segments without being detected, or indeed detectable, clinically.

That a similar phenomenon occurs in a definite group of patients with coronary thrombosis is clearly demonstrated by following the clinical and electrocardiographic findings. This occurs in the absence of surgery or other trauma, malignancy, and, in the strict sense, inflammation (at least without the basis of infection). These patients characteristically have a typical primary episode

*Recent unpublished work of Meyers and Poindexter suggests that minute increases in the prothrombin level of the blood may occur associated with coronary thrombosis.

followed at intervals of from seven to twenty-eight days or more by recurrent attacks of pain, fever, leucocytosis, and increased sedimentation rate, with electrocardiographic evidences of more marked involvement in the same area or multiple involvement in other areas of the heart.

Autopsy findings showing multiple undiagnosed occlusions of the coronary arteries also demonstrate that this phenomenon may occur without clinical recognition. Frequently a careful review of the history will reveal suggestive symptomatology which was not interpreted correctly by the patient or his doctor.

Do these multiple episodes of thrombosis occur because there exists a profound change in the thrombosing balance of the blood which is responsible for the first and the subsequent thrombi wherever the vascular walls are conducive to this process? Is the change primarily a local one which initiates a generalized change in the thrombosing balance of the blood? Or is it primarily a widespread vascular change which produces a condition conducive to thrombosis in numerous focal points at approximately the same time? We cannot answer these questions for either thrombophlebitis or coronary thrombosis at this time.

It is logical, from a physiologic viewpoint and on the basis of clinical experience in the treatment and prevention of venous thrombosis and pulmonary embolism, to utilize anticoagulant therapy for the treatment of coronary thrombosis where there is evidence of a tendency to additional thrombosis either local, scattered in the coronary tree, or mural. It should be pointed out that with the development of mural thrombi, thrombosis of the thebesian veins may occur as a result of obstruction of their ostia. Cases have been observed where the thrombi in the thebesian veins propagated into the larger venous sinuses. This sequence of events tends to further damage the myocardium by interference with its nutrition.¹⁸ This phenomenon is not as yet very widely recognized.

Dicumarol is the present drug of choice for this anticoagulant therapy. If the situation is very acute, heparin may be used for the first twenty-four to forty-eight hours until the action of dicumarol is established.

METHOD OF ADMINISTERING DICUMAROL

In our series the following techniques for administration have been used:

1. The prothrombin time is determined (Quick or Link-Shapiro undiluted technique⁶) before the first dose is given. The normal reading should be 13 to 17 seconds.
2. If the prothrombin time is normal or lower, 300 mg. of dicumarol are administered orally in one dose.
3. Each morning the prothrombin time is determined and reported to the physician in charge of the case *before* the dicumarol dosage for that day is determined.
4. Dicumarol is administered in 300 mg. doses daily until the prothrombin time is 30 seconds, and in 100 or 200 mg. doses when the prothrombin time is between 30 and 35 seconds on the upward portion of the curve.

*The thromboplastin used must be fresh and checked against a control for each test. The use of thromboplastin giving high control figures may prove dangerous in misguiding the dicumarol dosage.

5. When the prothrombin time reaches 35 seconds dicumarol is discontinued until it drops to below 30 seconds, when the drug may be given cautiously in 100 to 200 mg. doses again.

6. Daily prothrombin times are determined. Frequently the time may rise for several days after discontinuing dicumarol but will then return toward normal. If it reaches 60 or more seconds, hemorrhagic manifestations may occur. In this series, these were confined to minor purpuric spots in three patients.

7. If more severe hemorrhagic manifestations should occur, they may be checked by one or two whole *fresh* blood (may be citrated) transfusions of 300 to 500 c.c. each, by the administration of vitamin K (Menadione bisulfite, 64 mg., in from one to four doses has proved satisfactory), or both.

8. Dicumarol has been continued in most of these patients for thirty days after the last episode of thrombosis or embolism. The objective has been to keep the prothrombin time between 30 and 50 seconds especially during the first two to three weeks. The dosage is then tapered off slowly permitting the time to drop to 25 to 30 seconds followed by a gradual return to normal.

SUMMARY AND CONCLUSIONS

It would be premature to make extensive claims about the merits of dicumarol in the treatment of coronary thrombosis. Adequate controls with which to determine its value statistically are not yet available and will be of little value unless several subdivisions depending on the severity, extension, and complications of each group are studied separately. Each of these subdivisions must contain a statistically significant number of controls and treated patients. This will be a long and difficult but important evaluation.* It did not seem justified to await the final results of such a study before reporting on the experiences contained in this paper. We can conclude the following from these experiences.

1. In no case was there evidence that dicumarol aggravated or complicated the course of a patient with coronary thrombosis. The possibility that intimal hemorrhage^{19, 20} might be a complicating factor was considered, but no evidence was obtained in this series, either clinically or pathologically, that this was of significance in any case.

2. On the basis of previous animal and human experience with dicumarol, it appears physiologically sound to use it whenever there is a definite tendency for a thrombus to propagate or multiple thrombi or embolic phenomena to occur. Certain cases of coronary thrombosis demonstrate definite tendencies in this direction.

3. In numerous individual cases it has appeared that these thrombosing and embolic tendencies have been interrupted by the use of dicumarol. Considering the degree of pathologic narrowing of the coronary arteries found in some hearts, it is not surprising that occlusions did continue to occur in some patients on dicumarol therapy.

*Such a study is being planned as a cooperative venture in ten hospitals under the auspices of the American Heart Association.

4. The mortality rates for the complicated and the uncomplicated cases of coronary thrombosis treated with dicumarol appear to be lower than anticipated for each group, but it is considered inadvisable to draw conclusions regarding its effect on the mortality rate on the basis of so small a series and without careful controls. Another factor which may have influenced these figures favorably is the fact that the average age was younger than that usually considered average for patients with coronary thrombosis. Fifteen were under 35 years of age; only ten were above 60. Much more study is essential to determine this point.

5. In no instance was it felt that dicumarol influenced the rhythm or the rate of the heart directly.

This study suggests that dicumarol may be of value as a preventive measure against propagation, multiple serial attacks of coronary thrombosis within short spaces of time, mural and thebesian vein thrombosis, and embolic phenomena following coronary thrombosis. A study of the use of dicumarol in the treatment of such complications when associated with auricular fibrillation also seems justified. The value of the routine use of dicumarol in all cases of coronary thrombosis has been considered. The material available to date does not, however, justify the conclusion that dicumarol will affect the results in uncomplicated cases of coronary thrombosis.* It is also impossible to state to what degree it will affect the longevity of a patient with marked progressive arteriosclerosis of his coronary arteries. Further investigation with large groups of such patients will be necessary to determine the answer to these questions.

There is no evidence that once dicumarol has been discontinued and the blood prothrombin level has returned to normal any effect is exerted which decreases the risk of further attacks of coronary thrombosis in the same individual. Its continued use as a preventive measure may be a subject for future studies, but the risk of the use of this substance without careful frequent observation of the prothrombin level in the blood must be borne in mind.

REFERENCES

1. a. Campbell, H. A., Roberts, W. L., Smith, W. K., and Link, K. P.: Studies of Hemorrhagic Sweet Clover Disease. I. The Preparation of Hemorrhagic Concentrates, *J. Biol. Chem.* 136: 47, 1940.
- b. Campbell, H. A., Smith, W. K., Roberts, W. L., and Link, K. P.: Studies of Hemorrhagic Sweet Clover Disease. II. The Bioassay of Hemorrhagic Concentrates by Following the Prothrombin in the Plasma of Rabbit Blood, *J. Biol. Chem.* 138: 1, 1941.
- c. Huebner, C. F., and Link, K. P.: Studies of Hemorrhagic Sweet Clover Disease. VI. The Synthesis of the Delta-Diketone Derived From the Hemorrhagic Agent Through Alkaline Degradation, *J. Biol. Chem.* 138: 529, 1941.
- d. Link, K. P.: The Anticoagulant Dicumarol, *Harvey Lect.* 34: 162, 1943-44.
2. Bingham, J. B., Meyer, O. O., and Pohle, F. J.: Studies of the Hemorrhagic Agent, 3,3'-methylene-bis-(4-hydroxycoumarin); Its Effect on the Prothrombin and Coagulation Time of the Blood of Dogs and Humans, *Am. J. M. Sc.* 202: 593, 1941.
3. Butt, H. R., Allen, E. V., and Bollman, J. L.: A Preparation From Spoiled Sweet Clover, 3,3'-methylene-bis-(4-hydroxycoumarin) Which Prolongs Coagulation and Prothrombin Time of the Blood, *Proc. Staff Meet., Mayo Clin.* 16: 338, 1941.

*Since this paper has been prepared, two favorable reports have appeared, each based on fifty cases of coronary thrombosis treated with dicumarol, as follows: Nichol, E. S., and Page, S. W.: Dicumarol Therapy in Acute Coronary Thrombosis, *J. Florida M. A.* 32: 365, 1946; Peters, H. R., Guyther, J. R., and Brambel, C. E.: Dicumarol in Acute Coronary Thrombosis, *J. A. M. A.* 130: 398, 1946.

4. a. Prandoni, A., and Wright, I. S.: The Anti-Coagulants Heparin and the Dicoumarin-3,3'-methylene-bis-(4-hydroxycoumarin), *Bull. New York Acad. Med.* 18: 433, 1942.
- b. Wright, I. S., and Prandoni, A.: Dicoumarin-3,3'-methylene-bis-(4-hydroxycoumarin); Its Pharmacological and Therapeutic Action in Man, *J. A. M. A.* 120: 1015, 1942.
5. a. Lehmann, J.: Hypoprothrombinaemia Produced by Methylene-bis-(hydroxycoumarin); Its Use in Thrombosis, *Lancet* 1: 318, 1942.
- b. Idem: Hypo-Prothrombinemia Produced by 3,3'-methylene-bis-(4-hydroxycoumarin) and Its Use in the Treatment of Thrombosis, *Science* 96: 345, 1942.
6. a. Allen, E. V., Barker, N. W., and Waugh, J. M.: A Preparation From Spoiled Sweet Clover [3,3'-methylene-bis-(4-hydroxycoumarin)] Which prolongs Coagulation and Prothrombin Time of the Blood; a Clinical Study, *J. A. M. A.* 120: 1009, 1942.
- b. Barker, N. W., Cromer, H. E., Hurn, J., and Waugh, J. M.: The Use of Dicumarol in the Prevention of Postoperative Thrombosis and Embolism With Special Reference to Dosage and Safe Administration, *Surgery* 17: 207, 1945.
7. Wright, I. S.: Experiences With Dicumarol in the Treatment of Coronary Thrombosis. *Proceedings Amer. Fed. Clinical Research, first Far Western Meeting, Salt Lake City, Dec. 28, 1945.*
8. Baumgarten, P.: Entzündung, Thrombose, Embolie, und Metastase im Lichte neuerer Forschung, München, 1925, J. F. Lehmanns.
9. Dietrich, A.: Thrombose, ihre Grundlage und ihre Bedeutung, Berlin, Wien, 1932, Julius Springer.
10. Hueck, H.: Blood Proteins After Operation, *Arch. f. klin. Chir.* 136: 774, 1925.
11. von Seemen, H.: Operation und Gewebeschonung: Beziehungen zwischen Operationswunde und Entstehung, Vermeidung und Bekämpfung der mittelbaren Operationschädigungen (spontane Venenthrombose und Pneumonie), *Deutsche Ztschr. f. Chir.* 223: 85, 1930.
12. Stuber, B., and Lang, K.: Zur Pathogenese und Therapie der Thrombose, *Klin. Wchnschr.* 9: 1113, 1930.
13. Naegeli, Th.: Postoperative Thrombosis and Embolism, *Schweiz. med. Wchnschr.* 55: 520, 1925.
14. V. Seemen, H.: Quoted by Bruzelius (Ref. 17), *Verhandl. deutsch. Gesellsch. Chir.* 51: 41, 1927.
15. Löhr, W.: Quoted by Bruzelius (Ref. 17), *Deutsche Ztschr. f. Chir.* 183: 1923.
16. Starlinger, W., and Sametnik, S.: Ueber die Entstehungsbedingungen der spontanen Venenthrombose, *Klin. Wchnschr.* 6: 1269, 1927.
17. Bruzelius, S.: Dicoumarin in Clinical Use, *Acta chir. Scandinav.* 92: Supp. C, 1, 1945.
18. Flynn, J. E.: Personal communication.
19. Winternitz, M. C., Thomas, R. M., and LeCompte, P. M.: The Biology of Arteriosclerosis, Springfield, Ill., 1938, Charles C Thomas.
20. Horn, H., and Finkelstein, L. E.: Arteriosclerosis of the Coronary Arteries and the Mechanism of Their Occlusion, *AM. HEART J.* 19: 655, 1940.

THE NEUROVASCULAR SYNDROME AS MANIFESTED IN THE UPPER EXTREMITIES

COLONEL ROSS PAULL, M.C.
ARMY OF THE UNITED STATES

OVER a period of many years much has been written on vascular and neurological syndromes which result from anatomic anomalies in the neck and shoulder girdle. It is not the purpose of the author to review the literature dealing with these anomalies, nor to outline the differential diagnostic features. Wright⁸ has recently well provided this information in his article describing the neurovascular syndrome produced by hyperabduction of the arms (Figs. 1A, 1B, 1C, and 1D) in persons not necessarily having any anatomic anomalies in the neck or shoulder, such as extension of transverse processes and cervical ribs of the lower cervical vertebrae,¹⁻⁴ tendinous or cartilaginous extensions or counterparts of cervical ribs,⁵ scalenus anticus,^{5, 6} abnormal costoclavicular compression,^{3, 7} ruptured cervical nucleus pulposus, extrinsic or intrinsic tumor of the cervical cord, ulnar or median nerve injury, etcetera.

This case report describes a patient with complaints which, but for Wright's recent article,⁸ would very probably have been diagnosed as "scalenus anticus syndrome" only, while actually this represents an example of the "hyperabduction neurovascular syndrome" as well. This material is offered so that the latter syndrome may be more frequently in examiners' minds, more zealously sought for, more frequently recognized, and more properly treated. Certain observations and recommendations as to treatment may be worthy of consideration. Relief from long-standing symptoms rapidly followed after the treatment outlined was initiated in this case. The relief may, however, have been unrelated to or only partially due to the treatment.

CASE REPORT

A white man, 52 years of age, of temperate habits but for smoking two and a half packs of cigarettes daily, was unable to recall any illness, operations, or injuries which might have played a role in the precipitation of his present illness.

In January, 1943, while on Army transport duty he spontaneously and gradually developed a pain in the region of the distal anterior aspect of the right biceps muscle. This pain became extremely severe. It was unaccompanied by tenderness, paresthesia, hypesthesia, numbness, or tingling. Passive or active motion of the right humeroscapular and elbow joints and pronation or supination of the right forearm greatly aggravated the pain. Anodynes, heat, massage, and manipulation of the afore-mentioned joints failed to relieve this pain, but it gradually subsided, disappearing about April, 1943. In July, 1943, the pain spontaneously and gradually returned, this time bilaterally. It was not at this time aggravated by the motions which had proved aggravating from January to April, 1943. He now observed the pain to be aggravated bilaterally by allowing his shoulders to be depressed toward his hips while his arms were at his sides and to be more distressing at night than by day.

Received for publication Nov. 1, 1945.

The pain was now, as before, essentially constant with fluctuations in severity. It was partially relieved if, while sitting, the patient placed his elbows on a table or on the arms of a chair, and if, while lying prone, he allowed his forearms to hang over the sides of the bed toward the floor. His customary sleeping position had been the prone position with his arms hyperabducted above his head and approximately parallel to the longitudinal axis of the body (Fig. 1A). The symmetrical pains developing in July were from the onset accompanied by bilateral ulnar hypesthesia, bilateral median and ulnar numbness and tingling, essentially constant pain in the left forearm and hand, and recurring episodes during which

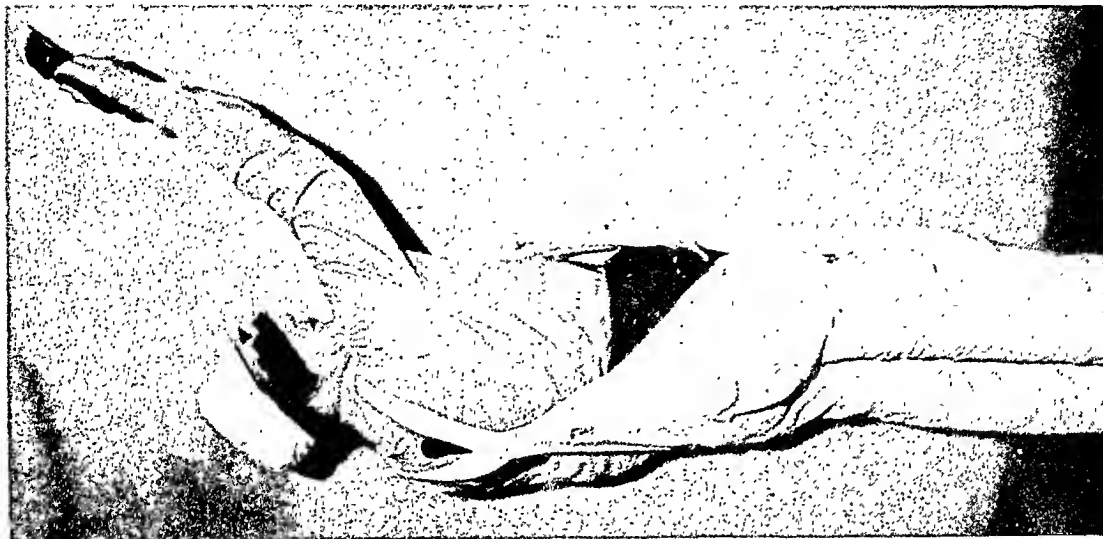


Fig. 1C.



Fig. 1A.

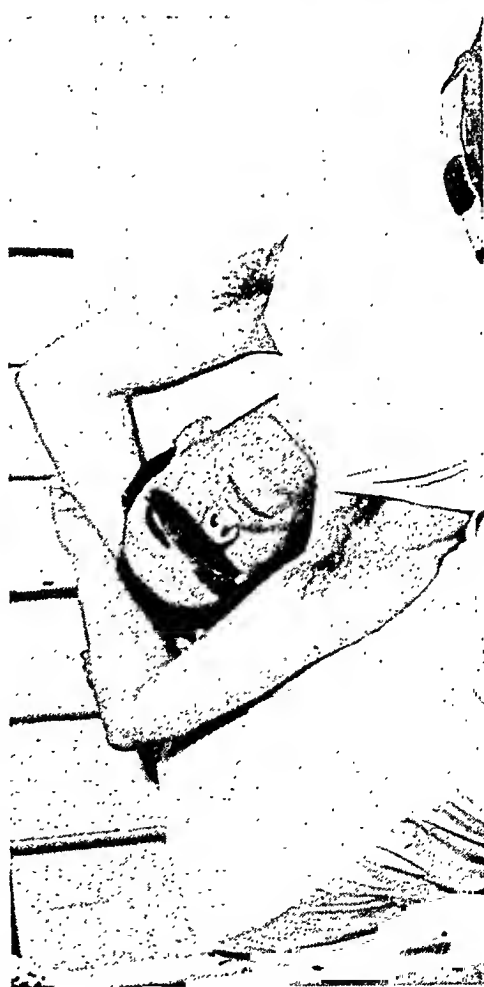


Fig. 1B.

Figs. 1A, 1B, and 1C.—For the purposes of this article these poses all portray what is described as hyperabduction of the arms. The word hyperabduction is herein used for lack of a more accurately descriptive term.

his left forearm felt cold. An extended course of generous doses of thiamine hydrochloride parenterally administered elsewhere had failed to give relief. The persistence of severity of the symptoms resulted in his hospitalization April 30, 1945.

The physical examination on this date revealed: (1) Hypesthesia over the areas innervated by the ulnar nerve, bilaterally; (2) obliteration of the right and reduction in amplitude of the left brachial pulse when the patient's arms were actively or passively hyperabducted (about 160 degrees) above his head when he was in the erect position (Fig. 1C); (3) obliteration of the right and reduction in amplitude of the left brachial pulse when the patient rotated his head to the left or right, respectively, with his arms abducted laterally 90 degrees from his body (less extreme rotation of the head was required to obliterate the pulses if the subject was obliged to rotate his head against the resistance of the examiner); (4) the development, in about three minutes, of bilateral ulnar numbness and tingling on the assumption of the positions portrayed in Figs. 1A, 1B, and 1C (this numbness and tingling developed even with a degree of hyperabduction insufficient to obliterate the radial pulses and regardless of whether the patient was erect, prone, or supine); (5) failure of the brachial pulse to return for two to five seconds after the obliterating positions had been abandoned, the interval increasing somewhat with extension of the time obliterating position had been maintained; (6) the shoulder girdles to be lightly muscled and normally or subnormally free in shoulder elevation and in hyperabduction of the arms.

Active or passive extreme depression of the shoulders with the arms at the sides failed to obliterate or reduce either brachial pulse; passive forcing of the shoulders posteriorward and downward failed to obliterate or reduce the amplitude of either brachial pulse.³⁻⁷ Unfortunately, the author forgot to determine if prolonged depression of the shoulders toward the hips or downward and posteriorward would produce symptoms. It would seem likely, however, that symptoms would have resulted, for the patient stated in his history that his arms and hands pained and tingled when permitted to hang at his sides when he was in the erect position. This pain and tingling was very favorably influenced by removing the weight of the upper extremities from his shoulders by resting his elbows on a table or the arms of a chair. No reflex changes were demonstrable. Oscillometric and surface temperature studies were not available.

X-ray studies of the cervical and thoracic spines revealed only a slight scoliosis in the region of the fifth thoracic vertebra, with the concavity to left. X-ray studies of the sinuses revealed a marked uniform density throughout the left antrum.

The blood count, blood Kahn, blood sedimentation rate, blood urea nitrogen, urinalysis, and x-ray studies of the heart and lungs were normal.

The symptoms and findings lead the examiner to the conclusion that the patient probably had both the scalenus anticus syndrome^{5, 6} and the "neurovascular syndrome produced by hyperabduction of the arms,"⁸ described by Wright. The amount of vascular element in the clinical features of this particular case is difficult to evaluate, for the brachial plexus, bilaterally, reacted to hyperabduction of a degree insufficient to obliterate the brachial pulses, and bilaterally reacted with the development of symptoms when the arms hung at the sides with the patient erect, though even an extreme of this latter position failed to obliterate either radial pulse. This case seemed not involved by the presence of a cervical rib. Whether or not a tendinous or cartilaginous band in the place of a rudimentary cervical rib was present⁶ and acted in the manner of its counterpart was not determined; that it was the chief causative factor appeared unlikely. A ruptured cervical nucleus pulposus could possibly be present and causative; this, too, appeared unlikely in the absence of x-ray evidence of such a condition. Wright⁸ reported that the obliteration of the radial pulse by hyperabduction of the arms is difficult and frequently impossible to produce in "loose jointed" individuals.

Since stretching or tension of the nerve trunks and brachial plexus is among the possible causes of the symptoms under study, it was decided to direct the patient to practice certain exercises and maneuvers which, it was believed, would possibly slowly lengthen the nerve and vascular structures, thus reducing the amount of tension to which they would be subjected and

THE NEUROVASCULAR SYNDROME PRODUCED BY HYPERABDUCTION OF THE ARMS

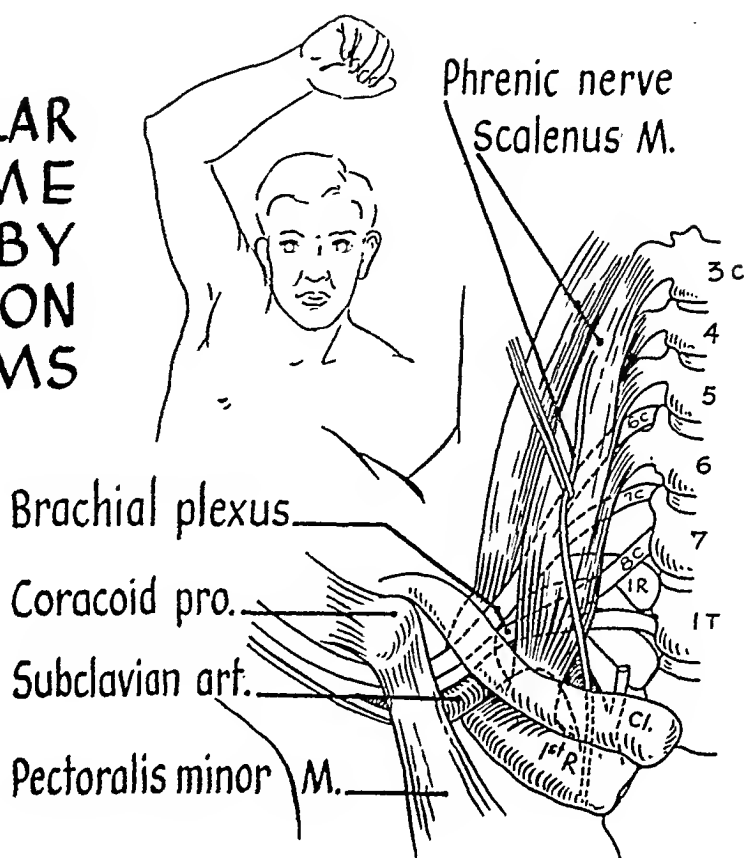


Fig. 1D.

ARM IN RELAXED ABDUCTION

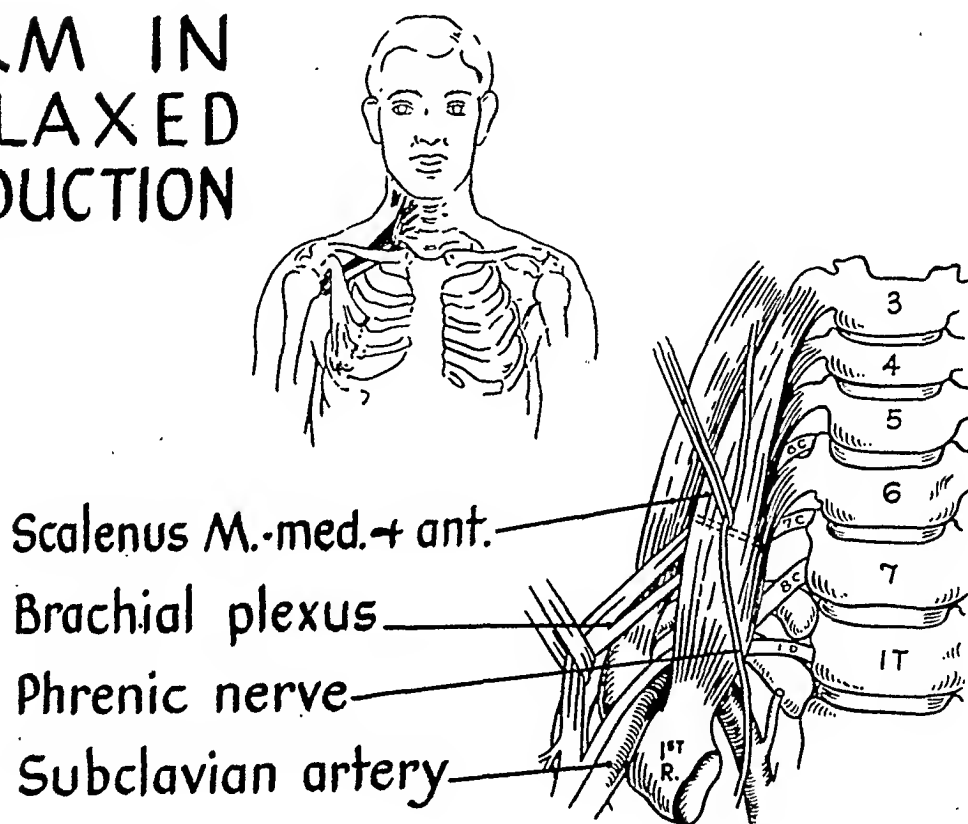


Fig. 1E.

Figs. 1D and 1E.—These figures are included for more graphic exhibition of anatomic relationships in various positions.

would make the patient's shoulder girdles more "loose jointed." By stretching out the musculofascial structures which limit the excursion of the lateral angle of the scapula toward the midline of the body and cephalad, one reduces the acuity of the angle around which nerve and vascular structures are stretched as they pass under the coracoid process when the subject's arms are hyperabducted. This same stretching would also tend to widen the costoclavicular space. The maneuver outlined to relieve the intolerance to the hyperabduction position consisted simply of the patient's suspending himself by closely approximated hands while he relaxed his shoulder girdle muscles (Fig. 2). He was to so suspend himself three or four times a day for such a period of time as comfort permitted. To build up the antagonists of the muscles we sought to stretch, the patient was directed, three or four times daily, while erect and with a 10- to 20-pound weight in each hand, to shrug or elevate his shoulders (Fig. 3).



Fig. 2.

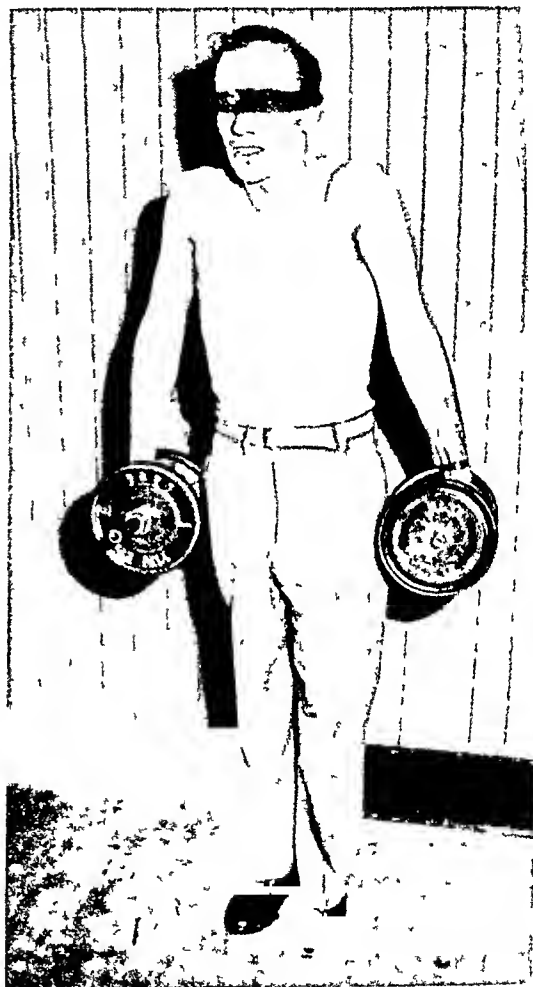


Fig. 3.

Fig. 2.—The position of suspension of the body by closely approximated hands, while shoulder girdle muscles are relaxed as completely as comfort permits.

Fig. 3.—The position of "shrugging" or elevating the shoulders against weighted resistance. The shoulders are actively elevated and passively relaxed or depressed alternately, thereby developing the elevators of the shoulders, better equipping them to hold the points of the shoulders higher without conscious effort.

If this patient's shoulders could be raised by developing the elevators of the shoulder, the acuity of the angle of the neurovascular structures as they pass through the angle formed by the first rib and the scalenus anticus muscle would be reduced. This should, it was believed, reduce the irritation to these structures at this musculoskeletal angle. Elevation

of the shoulder would also increase the costooclavicular space, lessening the hazard of pinching neurovascular structures at this point. These maneuvers and exercises were initiated about May 12 and were continued after the patient's discharge from the hospital, May 18, 1945. The patient was also directed to change his sleeping position to one in which his arms were not held in hyperabduction (Fig. 1A).

He reported improvement at the time of discharge, and on June 22, 1945, wrote, "My shoulders feel much better since taking the 'chinning' exercises. There is no pain in my left arm or hand. You will recall that when I was in the hospital, that was where I was bothered most. I still get the tingling sensation in the fingers in certain positions. My right wrist and right hand have bothered me and that appeared to be brought on by the chinning exercise. I appreciate the advice which I received about the shoulder exercises. I am continuing the exercises." About June 25 he reported by phone that the pain in his right wrist and hand had disappeared. On Sept. 1, 1945, the patient returned for re-examination. He then reported that the disturbing symptoms had disappeared and had not returned; that he had had no numbness or tingling in either arm or hand since about July 1; and that the pain earlier reported in the right wrist and hand still tended to recur infrequently, to last but a few days, and to develop and disappear gradually. The physical findings, September 1, were similar to those found April 30 on admission to the hospital except that the bilateral ulnar hypesthesia had disappeared and the shoulder girdles seemed more "loose jointed."

During his hospitalization in May, 1945, this patient exhibited keen interest as to the possible causative mechanisms and our aims in having him follow our suggested schedule of treatment. He has now quite completely abandoned his once customary sleeping position (prone with his arms in hyperabduction, Fig. 1A), and he now subconsciously rests his elbows on a table or chair arms when feasible. His new sleeping habits, his faithful exercise of the outlined treatment, or a combination of influences, some of which may not be clearly understood, may have produced the relief. This has occurred in spite of the persistence of certain physical findings which at the time of hospitalization seemed significant.

DISCUSSION

While the symptoms experienced by this patient probably resulted in part from obliteration of the arterial blood supply to the arms, it seems likely, in view of the prompt development of tingling in the fingers even when the arms were hyperabducted to a degree insufficient to obliterate the radial pulse, that changes in the nerve trunks resulted from prolonged stretching, pinching, or local ischemia, or some combination of these three factors. This does not, however, preclude the participation of arterial occlusion in the damage to the plexus and nerve trunks, for this patient's sleeping habits were such that he probably had pulseless brachial arteries for rather extended periods during his sleep. He habitually slept in the prone position and many, if not most, prone sleepers sleep with their arms in a position of hyperabduction and their faces turned toward one shoulder.

The obliteration of the brachial pulse by either the scalenus anticus syndrome or the hyperabduction syndrome may be due to either actual compression of the vessel so that its walls are opposed and lumen obliterated or to irritative spasm of the vessel. The fact that the radial pulse after obliteration does at times fail to return immediately on removal of the obliterating position or maneuver suggests that the latter is operative at times. This may explain Wright's observation⁸ that certain positions of the arm, though unchanged, are accompanied by sudden changes in the presence or absence of a palpable radial pulsation.

This case demonstrates that, in the same person, several variations in the mechanisms responsible for irritation or damage of neurovascular structures of the neck and axilla may exist. This individual is believed to have both the scalenus anticus and the hyperabduction syndrome, each syndrome possessing identical or very similar symptoms but produced by different means. The former syndrome is produced by the irritation and/or obliteration of neurovascular structures at the angle formed by the attachment of the scalenus anticus muscle to the first rib, the latter syndrome by abnormal costoclavicular compression, or by torsion, tension, or compression of the neurovascular structures at the point where they pass under the coracoid process and posterior to the pectoralis minor muscle, or by both mechanisms together.

SUMMARY

1. Neurological and vascular syndromes, singly or combined, caused by various anatomic anomalies and changes in the neck and shoulder region, have long been recognized. Similar or identical syndromes, caused by a functional mechanism (hyperabduction of the arms) in the absence of anatomic anomalies have more recently been recognized and described by Wright.⁸

2. The recently reported, functionally produced syndromes⁸ appear to be commonly produced (1) at the point where the vessels, plexus, and nerve trunks pass between the clavicle and first rib by costoclavicular pinching of the traversing structures, and (2) at the angle around which these structures pass under the coracoid process and posterior to the pectoralis minor, by torsion or stretching of the neurovascular structures. (Arterial spasm from irritation may in some cases contribute to the obliteration of the brachial pulse.)

3. Nonsurgical therapeutic suggestions, offered for consideration, are designed to: (a) avoid the positions responsible for the syndromes when practicable; (b) widen the costoclavicular space; (c) lengthen the involved neurovascular structures; (d) reduce the acuity of the angle these structures traverse as they pass under the coracoid process while the arms are hyperabducted; and (e) shorten the course traversed by these structures.

REFERENCES

1. Willshire: Referred to in Clinical Records, Supernumerary First Rib, *Lancet* 2: 633, 1860.
2. Jones, F. W.: On the Relation of the Limb Plexuses to the Ribs and Vertebral Column, *J. Anat. & Physiol.* 44: 377, 1910.
3. Murphy, Thomas: Brachial Neuritis From Pressure of the First Rib, *Australian M. J.*, 15: 582-585, 1910.
4. Howell, C. M. H.: A Consideration of Some Symptoms Which May Be Produced by Cervical Ribs, *Lancet* 1: 1702, 1907.
5. a. Naffziger, H. C.: Editorial: The Scalenus Syndrome, *Surg., Gynec. & Obst.* 64: 119, 1937.
b. Naffziger, H. C., and Grant, W. T.: Neuritis of the Brachial Plexus, Mechanical in Origin; The Scalenus Syndrome, *Surg., Gynec. & Obst.* 67: 722, 1938.
6. Craig, W. McK., and Knepper, Paul A.: Cervical Ribs and the Scalenus Anticus Syndrome, *Ann. Surg.* 105: 556, 1937.
7. Falconer, Murray A., and Weddell, Graham: Costoclavicular Compression of the Subclavian Artery and Vein, *Lancet* 245: 539, 1943.
8. Wright, I. S.: The Neurovascular Syndrome Produced by Hyperabduction of the Arms, *AM. HEART J.* 29: 1, 1945.

POTENTIAL VARIATIONS OF THE RIGHT AURICULAR AND VENTRICULAR CAVITIES IN MAN

HANS H. HECHT, M.D.
SALT LAKE CITY, UTAH

IN THE five cases which form the basis of this report, an attempt was made to trace the course of the action current of the human heart directly by means of intracardiac catheterization. This seemed desirable because some of the fundamental concepts of electrocardiography have been evolved primarily from pertinent animal experiments, and assumptions concerning the course of the action current in the human heart have been made merely by analogy. Briefly, any electrical current of action can be considered as a line or layer of electrical dipoles or doublets so arranged that electropositive forces (source) are immediately followed by electronegative charges (sink).^{1, 2} To electrical currents produced by the heartbeat, the laws which govern their flow in volume conductors have been applied.² It has been demonstrated that electrograms recorded from auricular muscle strips or from muscle in situ follow closely a predictable pattern based on formulas derived from such laws.²⁻⁴

The spread of impulses over and through cardiac muscle seems to be very similar in practically all species regardless of the presence of readily demonstrable conducting tissues.⁵ Presumably no striking differences exist between the spread of the action current in the human heart and in the hearts of other mammals. The clinical use of precordial leads, for example, is based on the essential similarity in that respect of experimental electrocardiograms, particularly those of dogs, to those of man. For the study of the detailed sequence of activation of auricular and ventricular heart muscle, records from the endocardial as well as from the epicardial surfaces are required. Many such studies have been reported since the early observations of Lewis⁶ and Lewis and Rothschild.⁷ The admixture of cavity potentials to the precordial and standard limb lead electrocardiograms of the dog has led to newer interpretations of the pattern of bundle branch block, myocardial infarction, and myocardial infarction complicated by bundle branch block.⁸⁻¹⁰ Again by analogy, the results of these observations on animals have been used in the interpretation of the abnormal human electrocardiogram.^{11, 12} Epicardial leads have occasionally been recorded from human hearts but the potentials from the auricular and ventricular cavities needed to provide the final proof of the similarity of the human action current to that of experimental animals are lacking. It has been suggested that unipolar

Read in part before the Annual Meeting of the American Federation for Clinical Research, Atlantic City, May 28, 1946.

Part of this investigation was supported by grants from the Fluid Research Fund of the Rockefeller Foundation, the Utah Copper Company Research Fund, and the Physicians' Research Fund of the University of Utah Medical School.

Received for publication Sept. 21, 1945.

*From the Department of Internal Medicine, University of Utah Medical School, and the Wm. J. Seymour Hospital, Eloise, Michigan.

records from the right arm (V_R) and from certain esophageal leads reflect variations in cavity potentials. Leads of this kind are taken from positions located approximately opposite the large vascular openings at the base of the heart. This permits the potential variations of the ventricular cavities to be transmitted to the right shoulder and the right arm, or to the esophagus.^{12, 15} The location of these leads with respect to cardiac muscle is such, however, that they cannot be expected to represent potential variations of purely intracardiac origin.

Cardiac and vascular catheterization through the antecubital veins, as practiced by Cournand and others, provides a relatively safe procedure for obtaining electrocardiograms from the right auricular and ventricular cavities and from the larger veins.¹⁶ In the following experiments a No. 9 radiopaque catheter was used through which a small enamel-coated copper wire was threaded. The end of the wire was soldered to a small lead pellet which fitted and all but completely occluded the small opening at the tip of the catheter. This unit constituted the exploring electrode. A central terminal was used as the indifferent electrode. Under local infiltration with novocain, a right or left antecubital vein, usually the basilic vein, was exposed. Under fluoroscopic control the catheter was inserted and gently pushed ahead until the tip of the electrode was found to lie in the desired position. The patients were given sedation. Those in cardiac failure received 0.5 Gm. of aminophylline intravenously prior to the exposure of the cubital vein. All patients received 25 to 50 mg. of heparin to lessen the chance of intravascular clotting. None of the patients complained of pain or of discomfort of any kind, even when the tip of the electrode was seen to rest against cardiac muscle. No reactions or aftereffects were encountered. All patients received prophylactic treatment with sulfadiazine for two days after the procedure. X-rays and electrocardiograms were recorded frequently and at regular intervals.

The present report deals with the results obtained in five subjects. There were two instances of right bundle branch block (one complicated by a myocardial infarction two years previously), one of left bundle branch block, one of left ventricular enlargement, and one instance of left ventricular enlargement with frequent auricular and ventricular extrasystoles (bigeminy). On all patients standard bipolar limb leads, unipolar limb leads (extremity potentials), and serial unipolar precordial leads were obtained either immediately before or after the procedure. In one instance serial esophageal leads were recorded. Simultaneous records of either Lead I or of precordial Lead V_1 were made whenever feasible.

The records may conveniently be discussed according to the location of the tip of the electrode as determined by fluoroscopy.

Superior Vena Cava.—In two instances a record was obtained before the electrode had entered the heart itself. Both were patients with considerable left ventricular enlargement (one with associated signs of left auricular distention). The records revealed primary negative deflections for P and QRS, with positive T waves. The P waves were approximately one-half the size of QRS complexes and were double-notched in both instances, especially so in the case showing

evidence of auricular enlargement. The size of the deflections was of the order of those usually seen in unipolar extremity potentials, and their shape was almost identical with that observed in unipolar right arm leads (Fig. 1).

Inferior Vena Cava.—In one instance the electrode slipped into the inferior vena cava and down into a hepatic vein. The potentials recorded from the inferior vena cava were similar to those obtained from the superior vena cava,

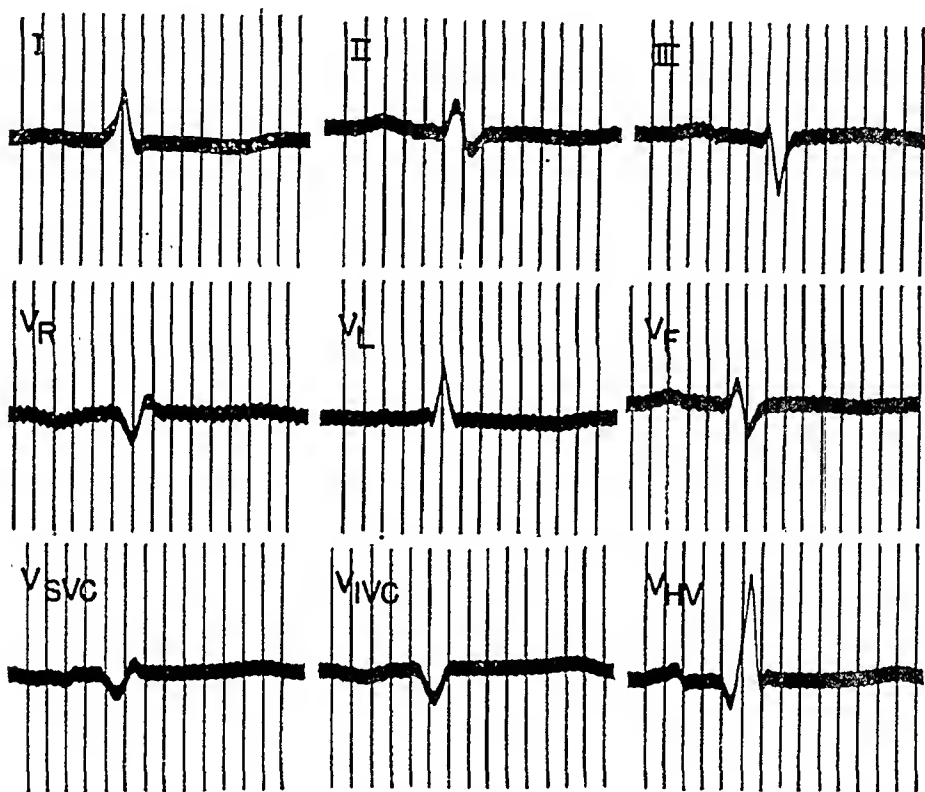


Fig. 1.—Leads I, II, and III, unipolar extremity potentials (V_R , V_L , V_F), and leads from superior vena cava (V_{SVC}), inferior vena cava (V_{IVC}) and from a hepatic vein (V_{HV}). Galvanometer sensitivity normal for standard lead and extremity potentials (augmented type), 0.75/N sensitivity for venae cavae and hepatic vein leads.

except that the auricular deflections were more rounded and the ventricular complexes lacked a small R wave which had been present before (Fig. 1). The record from the hepatic vein was quite different. A biphasic P wave was obtained, with a large slurred positive limb and a small negative spike. The ventricular deflections were primarily positive, displaying large R waves preceded by Q waves and followed by a small S deflection. The T waves were positive (Fig. 1). Neither the auricular deflections nor the ventricular complexes resembled those recorded in standard leads, extremity potentials (unipolar limb leads), or in any of six precordial leads. They were, however, of the left ventricular type, with a delayed peak of R (late onset of intrinsicoid deflection). The record appeared similar to those recorded by Helm, Helm, and Wolferth¹⁵ from the duodenum.

Right Auricle.—With the exception of the case mentioned above, the electrode entered the right auricle proper in all instances and records were obtained from various auricular levels.

1. *Auricular Deflections:* The auricular deflections appeared similar in configuration to those obtained from esophageal leads at auricular levels and were

of the same magnitude or slightly larger. Endocardial auricular waves are always biphasic and display a distinct QRS type of deflection, and are often followed by a plainly visible auricular T wave.* In one instance the electrode was found to be located inside the right auricle, adjacent to the entrance of the superior vena cava. A large, completely negative deflection was recorded (P_{qs}), indicating that the electrode very likely was located at the region of primary negativity, the sinus node (Fig. 2, A). When the electrode was moved toward the junctional region, there appeared a small P_R wave which gradually increased,

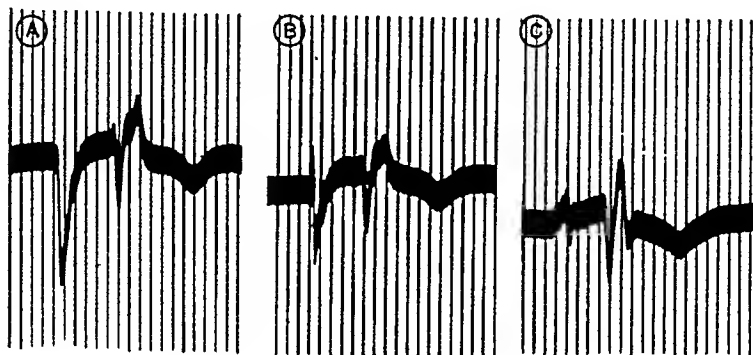


Fig. 2.—Case of right bundle branch block. (0.5/N sensitivity.) A, Large negative auricular deflection recorded from the immediate vicinity of the sinus node. B, Position of the exploring electrode slightly lower than in A: a small P_R wave has appeared, total voltage of P has decreased. Onset of intrinsic deflection for P occurs 0.005 second after beginning of P_{qs} . C, Low auricular position (junctional region): small P wave with broad P_R deflection. Onset of intrinsic deflection for P: 0.060 second after beginning of P_{qs} . Note change in contour of the ventricular deflection when the electrode is moved from upper to lower auricular levels.

so that at lower auricular levels a broad P_R , followed by a small sharp P_s deflection, was present (Fig. 2, B and C). A small P_R with a relatively large P_s was always noted in other records whenever the electrode was located in the upper auricular region (Figs. 3, C, 4, E, and 5, A). Occasionally the P_s deflection was broad: at times it completely occupied the space between the end of P and the beginning of QRS, which is usually isoelectric in standard limb leads (Fig. 3, C). Large P deflections with small or absent P_R are characteristic of upper auricular levels: large P_R waves with a decrease in the total voltage of P are typical of lower auricular or junctional levels. These findings are in agreement with those of Macleod and Cohn,¹⁷ who obtained endocardial leads in cats with a comparable technique. In one instance a biphasic P wave with a predominant P_R deflection was obtained when the electrode was situated in the vicinity of the tricuspid valves (Fig. 4, C). When an attempt was made to insert the electrode into the right ventricle, the electrode curled up and was finally found lying along the auricular septum, apparently in contact with the endocardial surface. A strikingly large biphasic auricular deflection was obtained

*Since the shape of the action currents recorded from the auricles does not appear to differ fundamentally from the shape of action currents recorded from the ventricles, it seems advisable to use a comparable nomenclature. Therefore, following the standard nomenclature for QRS, the terms P_q , P_{qs} , P_{qs} , P_R , P_s , and P_r have been introduced to facilitate the description of the complexes obtained.

In this paper, the auricular T wave is labeled P_r instead of T_a as has been suggested. P_r seems to be a more logical term than T_a , the derivation of which may not be readily understood.

The use of the terminology which is here proposed does not imply that the spread of the action current through auricular muscle is similar to the spread over the ventricular musculature.

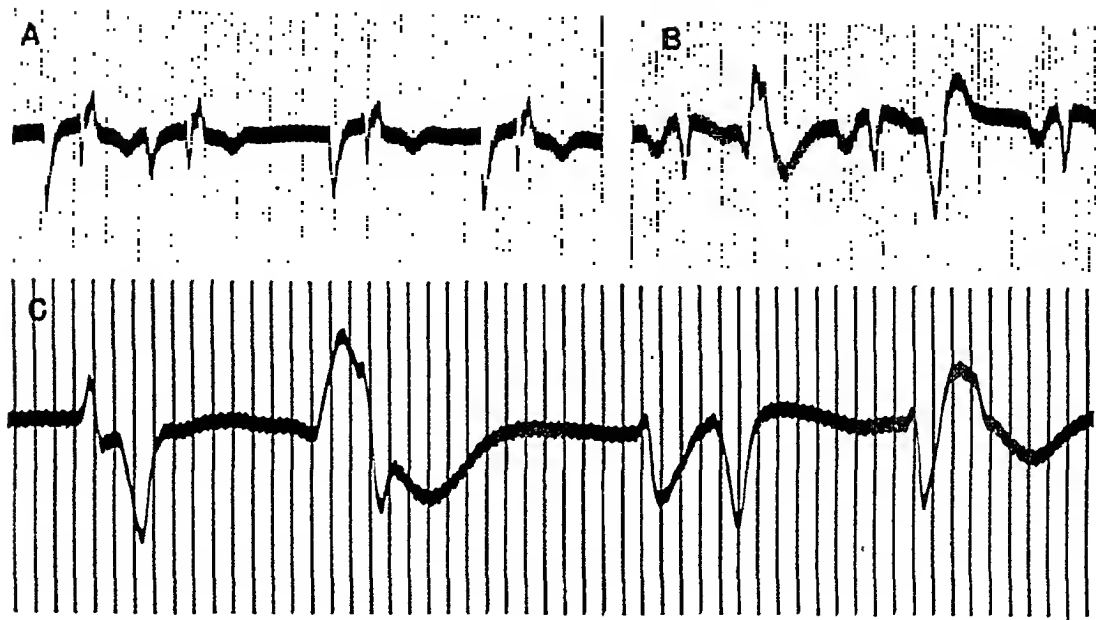


Fig. 3.—Auricular and ventricular extrasystoles. (0.5/N sensitivity.) *A*, Case of right bundle branch block (see Fig. 2), endocardial lead from the sinus regions. Deep P_{qs} deflections with sinus extrasystole (second beat) showing aberrant auricular response. *B*, Case of left ventricular enlargement. Upper auricular or lower superior vena cava lead. Beats 1, 3, and 5 are normal responses with deep QS deflections; Beat 2 is a left ventricular extrasystole (with large S waves in Lead I—not shown). Q wave transmitted from left ventricle, large R waves from right ventricular cavity. Beat 4 is an auricular extrasystole with abnormal P wave and a broad QS deflection (right ventricular cavity). *C*, Same case as *B*. Endocardial lead from upper auricular level. The third beat is a normal complex with a small P_r , deep P_s , and deep QS deflection. Beat 1: Auricular (nodal?) extrasystole with short P-R interval, abnormal P, and deep QS. Beat 2: Left ventricular extrasystole with large R (right ventricular cavity). The small "S wave" appears to be the final portion of a P_{qs} superimposed upon a ventricular complex. Beat 4 represents again a left ventricular extrasystole with a P_{qs} immediately preceding it. The early part of QRS is superimposed upon the ascending limb of P_s .

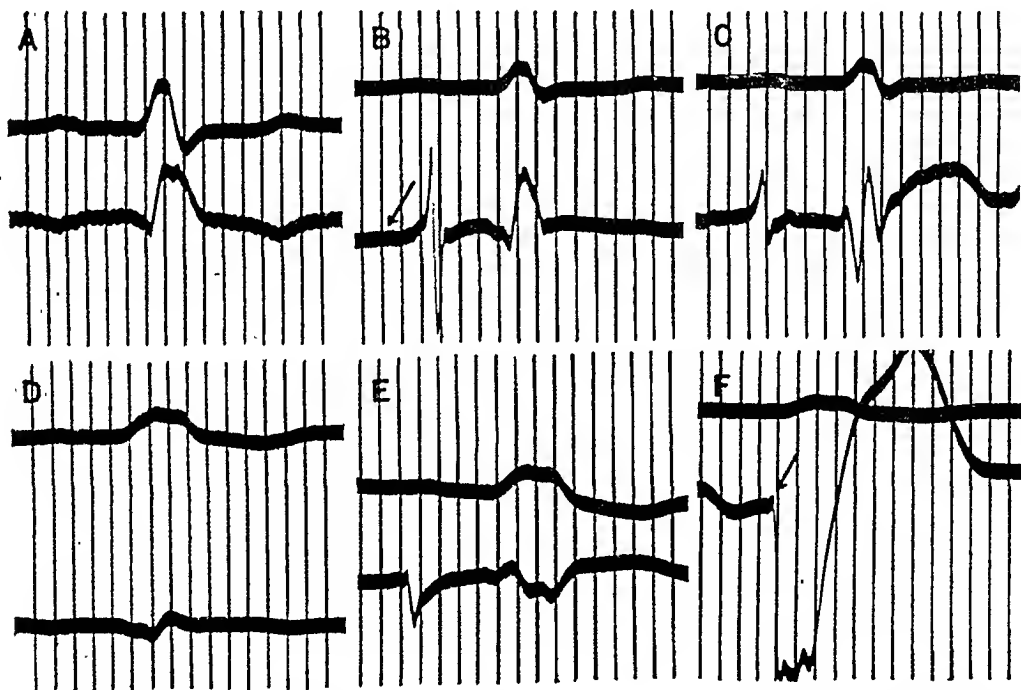


Fig. 4.—*A*, *B*, and *C*: right bundle branch block. *D*, *E*, and *F*: left bundle branch block. *A*, Lead I and V_n (2/N sensitivity). *B*, Lead I and electrogram from right auricle (0.9/N sensitivity). Arrow points to small preauricular deflection. Note P_r distorting the P-R interval. *C*, Lead I and endocardial lead from lower auricular levels (0.9/N sensitivity). Some distortion by artifacts. *D*, Lead I and V_n (2/N sensitivity). *E*, Lead I and endocardial lead from upper auricular level. Note preauricular deflection and small P_n . *F*, Lead I and endocardial lead from right ventricle (0.15/N sensitivity). Arrow points to small preintrinsic deflection of QRS.

which displayed a classic intrinsic deflection. Its onset appeared 0.065 second after the beginning of the auricular deflection (Fig. 4, *B*). In this case, high-speed records revealed a small, positive preauricular deflection immediately preceding the onset of P_R and occurring almost 0.05 second before the onset of P in a simultaneously recorded standard bipolar lead. A similar deflection was found in one other instance (Figs. 4, *E*, and 5, *A*).

Auricular extrasystoles showed either increased or decreased P_R deflections, when compared with the pattern of the normal beats for that region. A sinus extrasystole recorded with the electrode placed at the sinus region showed a deep but splintered P_{QS} deflection (Fig. 3, *A*).

2. Ventricular Deflections: Records from lower right auricular levels, taken with the electrode in the vicinity of the tricuspid valves (beneath or just to the right of the sternum), should represent potential variations of the right ventricular cavity which were transmitted through the atrioventricular opening. At higher auricular levels, the electrode is situated behind and above the ventricles and may conceivably deflect a mixture of potential variations of the right and left ventricular cavities and of endocardial action currents from both ventricles. A striking similarity was always noted between ventricular complexes recorded at high auricular levels and those recorded in a unipolar right arm lead (V_R). These records usually differed from those obtained from lower auricular or ventricular levels, particularly when bundle branch block was present (Figs. 1, 4, and 5).

The two individuals with normal ventricular activation (left ventricular enlargement) displayed deep Q-S deflections from all auricular levels, followed by small, positive T waves, often with slight elevation of the S-T segment (Figs. 1 and 3, *B* and *C*). In left bundle branch block a somewhat similar record was obtained. The QRS deflection was represented as a deep negative deflection throughout ventricular excitation, except for an earlier portion partly preceding the beginning of QRS in a simultaneously registered Lead I. The record displayed a small Q and a small R, followed by a broad and notched S (Figs. 4, *E*, and 5, *A*). The duration from the beginning of Q to the top of R measured 0.055 second; the S wave from the top of R to S-T junction, 0.125 second. The total duration of QRS in the standard limb Lead I measured only 0.165 second; in endocardial leads the duration of QRS was 0.180 second.

Records taken from the upper auricular levels of the two subjects with right bundle branch block were similar in most details to those obtained from the right arm of these subjects (Figs. 2, *A* and *B*, 3, *A*, and 4, *B*). In the first case a small R wave preceded a rapid downward deflection, after which a broad, notched R' wave occurred which occupied more than half the total duration of QRS (Figs. 2, *A* and *B*, and 3, *A*). The small R wave was not present in a record taken from the lower auricular level, and a short but deep Q wave was noted, followed by a slightly notched R deflection. The peak of R appeared 0.04 second earlier than in upper auricular records (Fig. 2, *C*). In the second case a similar difference was noted: the record taken from the posterior aspects of the auricle was similar to V_R and displayed a small Q wave followed by a broad and notched R wave (Fig. 4, *B*). The complexes taken in the vicinity of

the tricuspid valve showed a small R, a deep S, a large R', and a small S'. In this case, the peak of R' occurred later than that of R in upper auricular records (Fig. 4, C).

Frequent ventricular extrasystoles were noted in one case. Because the extrasystoles displayed a conspicuous S wave in Lead I, they were thought to have arisen within the left ventricle. Both upper and lower right auricular records revealed large positive deflections without a trace of Q or S waves. Premature auricular extrasystoles without aberrant ventricular responses always displayed a conspicuous downward ventricular deflection (Fig. 3).

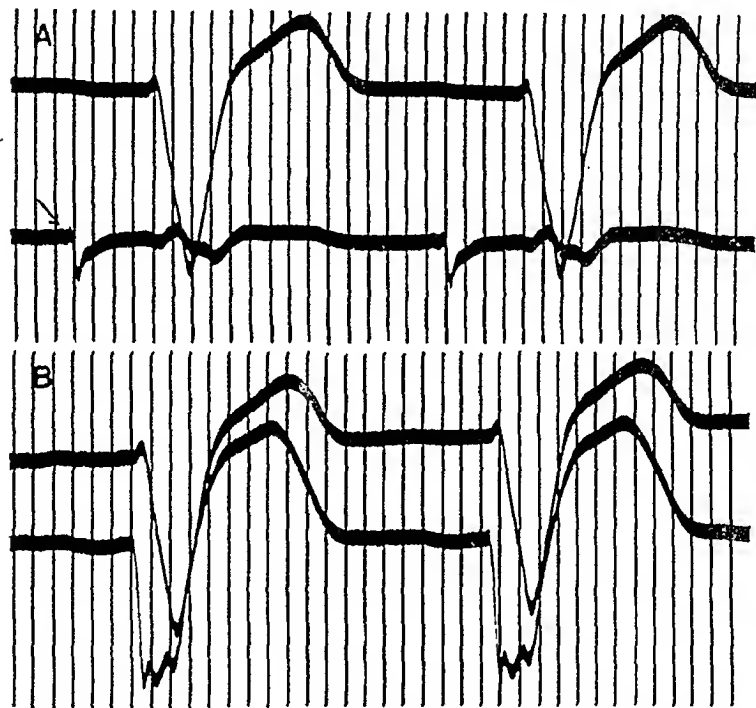


Fig. 5.—Left bundle branch block. A, Chest lead V_1 (0.5/N sensitivity) and endocardial lead from upper auricular level (0.5/N sensitivity). Arrow points to small preauricular deflection. B, Chest lead V_1 and endocardial lead from right ventricle (0.15/N sensitivity).

Right Ventricle.—In one patient with left bundle branch block, the right ventricle was entered and the tip of the electrode was found to be located to the left of the sternum, in the apical region. The voltage of QRS was about eight times higher than that observed in the auricles, while the P waves all but disappeared and became quite similar to the small, rounded deflections usually seen in standard limb leads and in precordial leads (Fig. 5, B). The ventricular deflections seemed to be primarily negative, but a small, diminutive R wave was noted which showed some phasic variation in height. On the average, the top of the R wave was recorded 0.003 second after the beginning of QRS. The R wave was followed by a deep and notched S deflection comprising almost the entire time of QRS. A large positive T wave followed. The downstroke of S coincided with the rise of R in a simultaneously recorded precordial lead V_1 . A large, positive T wave was recorded, its peak preceding the peak of T in the precordial lead (Fig. 5, B). The intrinsicoid deflection (top of R) in V_1 occurred 0.022 second after the beginning of the activation of the endocardial surface. Considering the approximate thickness of the right ventricle to have been

5 mm. (slight hypertrophy) in this case, the speed of the action current through the ventricular wall would have been about 300 mm. per second.

DISCUSSION

The studies which have been presented can be regarded only as preliminary observations which need further amplification. However, some of the records which were obtained strongly support our present concepts of cardiac excitation. In this respect, three observations are of particular interest. (1) Large, predominantly negative auricular deflections are encountered at high auricular levels, and distinct P_R waves appear either when auricular extrasystoles are encountered or when the electrode is moved toward the junctional region. (2) Ventricular complexes from the junctional auricular region show negative deflections in a normally activated heart and in left bundle branch block, and show positive deflections in right bundle branch block and in left ventricular extrasystoles. (3) Ventricular complexes recorded from higher auricular levels differ from those taken at lower levels and from the right ventricular cavity. They are quite similar, however, to those which are obtained when the exploring electrode is placed on the right arm (V_R).

Auricular Activation.—The finding of an area of primary negativity in the vicinity of the opening of the superior vena cava is in keeping with Lewis' observation on the location of the cardiac pacemaker in dogs.⁶ The absence of an early P_R wave is also noted in records taken from the venae cavae (Figs. 1 and 3, *B*), but the sudden and striking increase in magnitude of the deflection in the case illustrated in Fig. 2 favors the assumption that the exploring electrode must have rested close to a point which remained throughout the auricular cycle electronegative with respect to the surrounding tissue. Whatever theory is accepted, the region from which the impulse originates must always be negative to adjacent muscle. If it is assumed that the spread of the action current is characterized by a crest of positive charges immediately followed by a negative wake, the region responsible for the release of impulses must always face the electronegative wake. This region will never become positive with respect to other parts of the cardiac muscle, and an electrode placed near this region will never record a positive deflection unless the point of impulse formation has shifted. For this reason it can be assumed that the record obtained represents the potential variations of the sinus region.

A premature beat arising from this region (a sinus extrasystole) may at times find part of the auricular muscle still refractory; under these conditions an aberrant response of auricular tissue in the face of an otherwise normal activation will be obtained (Fig. 3, *A*). This should result in an abnormal P wave in standard limb leads. For standard limb leads, a sinus extrasystole is defined as a premature complex whose individual components, including P , are identical with the sinus beats. This statement should be modified, as an abnormal P might be expected to occur in standard limb leads if the new impulse falls in the recovery phase of the preceding beat. Unfortunately no simultaneous records of standard leads were made in the example shown in Fig. 3, *A*.

When the electrode is moved away from the point of primary negativity, a small P_R wave can be recorded which gradually increases in size. The preponderance of P_R over P_S increases with the distance of the exploring electrode from the sinus region. This observation favors another concept of auricular activation, which maintains that, in contrast to the manner of activation of ventricular musculature, the auricles are activated radially from the primary point of stimulation, similarly to the radial spread of waves emitted by a radio sender or by a stone thrown into a lake. The auricular electrogram which was recorded in one instance (Fig. 4, *B*) differed in no way from many experimental records obtained from isolated auricular muscle strips of the frog or turtle,^{3, 4} or from the epicardial auricular records of the dog obtained in situ.² The similarity of the P-wave pattern in certain esophageal leads to that in auricular endocardial leads is quite striking, and was noted by Macleod and Cohn.¹⁷ In any type of auricular muscle tissue no essential difference between endo- and epicardial records can be expected if the action current spreads radially from its point of origin. Both types of records (endocardial and esophageal) can be considered as leads taken from a simple sheet of muscle submerged in a conducting medium. The intrinsic deflection for P_R appears later in esophageal leads than in endocardial right auricular leads. This indicates merely that the distance of the exploring electrode from the point of primary negativity is greater in esophageal leads than in right auricular endocardial leads.

A small, rounded, positive deflection which definitely preceded any other evidence of auricular activation was occasionally recorded (Figs. 4, *B* and *E*, and 5, *A*). This "preauricular deflection" may be a normal constituent of the human electrocardiogram which, because of its smallness, has hitherto escaped detection in the conventional leads. Its significance is doubtful but it resembles in contour and magnitude, though not in direction, the "prepotentials" which have been recorded by Bozler under a variety of conditions. Bozler believes that these potential oscillations might initiate normal sinus discharges.¹⁸

Ventricular Activation.—No similarity of the electrocardiographic pattern is present when the ventricular complexes from the endocardial surfaces are compared with "epicardial" leads from the precordium or from lower esophageal levels. Deep Q-S deflections are obtained from the right auricular and ventricular cavities when conduction of impulses occurs over the intact His bundle either in normal sinus beats or in auricular extrasystoles with normal ventricular responses. This again is in agreement with Macleod and Cohn's observation,¹⁷ and with open-chest experiments on animals where a needle electrode is thrust through the musculature into the ventricular cavities.⁸ On the basis of these experiments, the characteristic Q waves of myocardial infarction have been explained as denoting the appearance of potential variations of the ventricular cavities at the epicardial surface which are transmitted through electrically inert infarcted and fibrosed areas.^{9, 10, 12} The demonstration of cavity potentials of a similar kind in man makes the explanation of QRS changes associated with myocardial infarction directly applicable to human records.

The small, quite variable R wave noted at the beginning of QRS inside the right ventricular cavity in a case of left bundle branch block is of interest.

The peak of this deflection occurs 0.003 second after the beginning of ventricular excitation and precedes considerably the onset of QRS in simultaneous standard leads (Figs. 4, *F*, and 5, *B*). A small preintrinsic deflection of this kind has been previously recorded in animal electrocardiograms from the right ventricular cavity.^{8, 17} In Wilson's record this deflection disappeared after left bundle branch block was produced. This experiment indicated that with a normally conducted impulse the left side of the septum was activated slightly in advance of the right. For the curves presented by Wilson, Hill, and Johnston, and also for those reported by Macleod and Cohn, this explanation appears logical and is strongly supported by reports of vector analysis of standard limb leads in human records.^{19, 20} The mode of activation of the intraventricular septum apparently varies, however, and in a number of records from various animals, activation of the right ventricle was found to precede slightly that of the left.⁵ In the record presented in Figs. 4, *E*, and 5, *B*, left bundle branch block was present, and activation of the septum must have occurred from right to left. Consequently the deflection cannot be ascribed to early activation of the left ventricular side of the septum. The assumption of Macleod and Cohn,¹⁷ that R waves of this kind from the right ventricular cavity may be caused by the expanding polarization of the left ventricle after the activation of the right has been completed, appears unlikely on anatomic grounds, since it assumes that the long axis of the left ventricle exceeds that of the right to a considerable degree. At present no satisfactory explanation can be offered for this small preintrinsic deflection unless it represents activation of parts of the endocardial surface at the base of the right ventricle, and of papillary muscles. These areas are presumably activated after the activation of the apical region. The action current speeds from apex to base during the extremely short period of radial excitation of the endocardial surface; this may account for a small period of positivity similar to the much longer period of positivity found in auricular muscle.

Except for the greater width of the complexes, there is no essential difference in the activation of the right ventricle in normally activated hearts and in those displaying left bundle branch block, since polarization of the right ventricular cavity is not influenced by the altered activation of the left. The right ventricular endocardial electrocardiogram obtained in the case of left bundle branch block (Figs. 4, *E*, and 5, *B*) can be taken as representing the normal pattern of endocardial activation of the right ventricle.

The tracings obtained from cases of right bundle branch block differ essentially from those discussed before. Right bundle branch block records displayed prominent positivity during most phases of ventricular activation (Figs. 2, 3, and 4). This is to be expected if one assumes that in instances of right bundle branch block the septum and the right ventricular cavities are being activated from the left ventricle, and that therefore a layer of positive charges faces the right ventricular cavity during the major part of ventricular excitation. The occasional biphasic QRS complexes which were observed have their analogue in animal experiments. This, it seems, indicates a radial spread of the action current over the endocardial surface after the impulse has reached the right ventricular cavity through the intraventricular septum and before it assumes and completes its course through the lateral ventricular walls.

In the face of overwhelming evidence in support of the new nomenclature of bundle branch block, it need hardly be mentioned that cavity potentials of the type recorded in man in intraventricular block could be obtained only if, in records of the first type (Figs. 4, *D*, *E*, and *F*, and 5), activation is normal in the right and delayed in the left ventricle (left bundle branch block); and if, in records of the latter type, it is delayed in the right but presumably normal in the left (right bundle branch block) (Figs. 2, 3, *A*, and 4, *A*, *B*, and *C*). The human records which have been presented are in accord with records of certain pertinent animal experiments which have been based on the assumptions that the action currents of the heart muscle may be represented as electrical doublets, or as an electrical source followed immediately by an electrical sink, that they follow the laws which govern the flow of electrical currents in volume conductors, and that the pathways which the action current traverses are identical to those worked out over many years for various species of mammalian and nonmammalian hearts.

The Meaning of V_R .—It remains to explain the more complex ventricular records which are obtained when the exploring electrode is situated at upper auricular levels. It has been pointed out that the ventricular complexes recorded from this region are quite similar to, and sometimes identical with the so-called unipolar leads from the right arm. They differ from tracings obtained from lower auricular or ventricular levels in cases of right or left bundle branch block but are similar to records from lower auricular levels in normally activated hearts. It has been stated that the right arm potentials (V_R) represent potential variations of the ventricular cavities transmitted to this region by the large vascular openings at the base of the heart.^{12, 13} It now appears that certain modification of this statement can be made. The auricular deflections in V_R are unlike the deflections in records made from the auricular endocardial surface but are similar to the deflections obtained when the electrode is located extracardially in one of the venae cavae (Fig. 1). The ventricular deflection in V_R is similar to that of endocardial records from the upper, but not from the lower auricular region. When the electrode is placed in the upper auricular position, the tip lies to the right and above both ventricular cavities and the intraventricular septum (Fig. 6, *B*). This position favors the recording of a mixture of potential variations from the basal parts of both cavities. In a normally activated heart, the potential variations of both cavities are negative, and consequently a deflection of QRS directed chiefly downward will be recorded regardless of whether the electrode records the potential variations of one or of two ventricular cavities. In left bundle branch block, the potential variations of the left ventricle are positive for the same reason that, in right bundle branch block, those in the right ventricle are positive. An electrode placed above and to the right of both ventricles will record a mixture of the positive potentials of the left and the negative potentials of the right ventricular cavity. As the right ventricle is closer to the exploring electrode, the effects of the right ventricular cavity will manifest themselves to a greater extent than those of the left, and the major portion of the electrocardiogram will show negative deflections. This preponderance of negativity will be particularly evident during the

later phase of activation, when the left ventricular cavity likewise becomes negatively charged as the impulse spreads through the lateral ventricular walls. Under these conditions a mixed record of the type obtained in Fig. 4, *E*, results. In right bundle branch block, early negative deflections with final broad R waves are typical for a right arm lead (V_R) and have likewise been recorded from upper right auricular levels (Figs. 2, 3, *A*, and 4, *A* and *B*). Again it seems likely that primary negative left ventricular potentials are responsible for the early part of QRS and that the large slurred R waves of the later phase are a reflection of the positive QRS complexes of the right ventricular cavity. Fig. 6 illustrates diagrammatically the position of the exploring electrode in relation to the potential variations of both ventricular cavities.

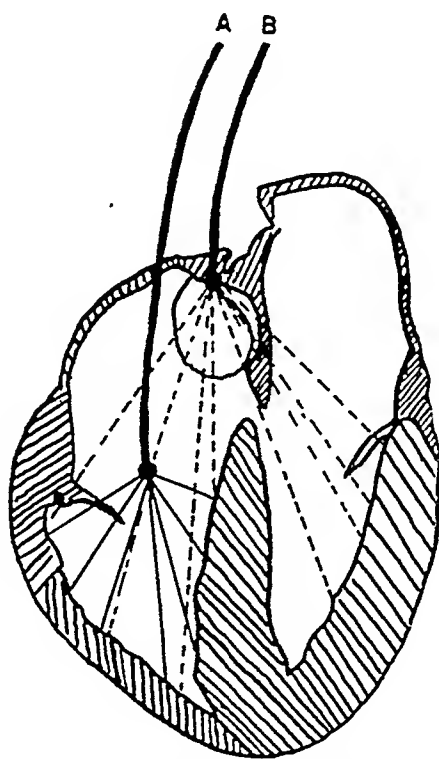


Fig. 6.—The relationship of the exploring electrode to the auricular and ventricular cavities. In position *A* the electrode is placed low in the right auricle. Position *B* is at a higher auricular level and therefore permits the recording of the potential variations of both right and left ventricular cavities (see text). The circle in the right auricle indicates the position of the inferior vena cava.

SUMMARY

1. Electrocardiograms from the endocardial surfaces of the right side of the heart and from the large veins have been obtained by means of a catheter-like electrode inserted through the right or left ante-cubital veins.

2. The potential variations which have been recorded are in agreement with the basic concepts of origin, spread, and distribution of the action current of the heart upon which modern electrocardiographic interpretation is based. The conclusions which have been drawn from animal experiments can safely be applied to human electrocardiography.

3. The potential variations recorded from unipolar right arm leads represent auricular deflections similar to those present in the large veins. The ventricular deflection in V_R is a faithful reproduction of records obtained from the endocardial surface of the upper portion of the right auricle. They represent a mixture of potentials from the right and left ventricular cavities.

Miss Jeanette Lelonde gave valuable assistance.

REFERENCES

1. Craib, W. H.: The Electrocardiogram, London, 1930, Medical Research Council, Special Report Series No. 147.
2. Wilson, F. N., Macleod, A. G., and Barker, P. S.: The Distribution of the Currents of Action and of Injury Displayed by Heart Muscle and Other Excitable Tissues, Ann Arbor, 1933, University of Michigan Press.
3. Macleod, A. G.: The Electrogram of Cardiac Muscle: an Analysis Which Explains the Regression or T Deflection, *AM. HEART J.* 15: 165, 1938.
4. Bayley, R. H.: The Potential Produced by Cardiac Muscle. A General and a Particular Solution, *Proc. Soc. Exper. Biol. & Med.* 42: 699, 1939.
5. Harris, A. S.: The Spread of Excitation in Turtle, Dog, Cat and Monkey Ventricles, *Am. J. Physiol.* 134: 319, 1941.
6. Lewis, Th.: Galvanometric Curves Yielded by Cardiac Beats Generated in Various Areas of the Auricular Musculature. The Pacemaker of the Heart, *Heart* 2: 23, 1910.
7. Lewis, Th., and Rothschild, M. A.: The Excitatory Process in the Dog's Heart: the Ventricles, *Phil. Tr., Lond. Series B* 207: 247, 1916.
8. Wilson, F. N., Hill, I. G. W., and Johnston, F. D.: The Interpretation of Galvanometric Curves Obtained When One Electrode Is Distant From the Heart and the Other Near or in Contact With the Ventricular Surfaces. II. Observations on the Mammalian Heart, *AM. HEART J.* 10: 163, 1934.
9. Johnston, F. D., Hill, I. G. W., and Wilson, F. N.: The Form of the Electrocardiogram in Experimental Myocardial Infarction. II. The Early Effects Produced by Ligation of the Anterior Descending Branch of the Left Coronary Artery, *AM. HEART J.* 10: 889, 1935.
10. Rosenbaum, F. F., Erlanger, H., Cotrim, N., Johnston, F. D., and Wilson, F. N.: The Effects of Anterior Infarction Complicated by Bundle Branch Block Upon the Form of the QRS Complex of the Canine Electrocardiogram, *AM. HEART J.* 27: 783, 1944.
11. Johnston, F. D., Wilson, F. N., and Hecht, H.: The Precordial Electrocardiogram in Myocardial Infarction Complicated by Bundle Branch Block, *J. Clin. Investigation* 18: 476, 1939.
12. Wilson, F. N., Johnston, F. D., Rosenbaum, F. F., Erlanger, H., Kossmann, C. E., Hecht, H., Cotrim, N., Menezes de Oliveira, R., Scarsi, R., and Barker, P. S.: The Precordial Electrocardiogram, *AM. HEART J.* 27: 19, 1944.
13. Kossmann, C. E., and Johnston, F. D.: The Precordial Electrocardiogram. I. Potential Variations of the Precordium and of the Extremities in Normal Subjects, *AM. HEART J.* 10: 925, 1935.
14. Wilson, F. N., Johnston, F. D., Cotrim, N., and Rosenbaum, F. F.: Relations Between the Potential Variations of the Ventricular Surfaces and the Form of the Ventricular Electrocardiogram in Leads From the Precordium and the Extremities, *Tr. A. Am. Physicians* 56: 258, 1941.
15. Helm, J. D., Helm, G. H., and Wolferth, C. C.: The Distribution of Potentials of Ventricular Origin Below the Diaphragm and in the Esophagus, *AM. HEART J.* 27: 755, 1944.
16. Cournand, A., and Ranges, H. A.: Catheterization of Right Auricle in Man, *Proc. Soc. Exper. Biol. & Med.* 46: 462, 1941.
17. Macleod, A. G., and Cohn, A. E.: A New Piezoelectric Manometer to Record Intracardiac Pressures and for the Simultaneous Recording of Intracardiac Electrograms, *AM. HEART J.* 21: 345, 1941.
18. Bozler, E.: The Initiation of Impulses in Cardiac Muscle, *Am. J. Physiol.* 138: 273, 1943.
19. Bayley, R. H.: Theoretical Genesis of Q as Observed in the First Three Standard Leads of the Electrocardiogram: a Preliminary Report, *J. Trop. Med.* 41: 144, 1938.
20. Gardberg, M., and Ashman, R.: The QRS Complex of the Electrocardiogram, *Arch. Int. Med.* 72: 210, 1943.

CLINICAL PICTURE AND TREATMENT OF THE LATER STAGE OF TRENCH FOOT

MAJOR DAVID I. ABRAMSON, M.C., CAPTAIN DAVID LERNER, M.C.,
LIEUTENANT COLONEL HARRIS B. SHUMACKER, JR., M.C., AND
LIEUTENANT COLONEL FORD K. HICK, M.C.
ARMY OF THE UNITED STATES

INTRODUCTION

DURING World War I, the single winter campaign in which the Ground Forces of the United States were involved resulted in approximately 2,000 cases of trench foot. In World War II, casualties of this type have been considerably greater due to the fact that a far larger Army took part in a number of winter campaigns.

A large proportion of the soldiers with trench foot have already returned to civil life, while those still in the Army will also be leaving in the near future as demobilization takes place. As a result, the burden of continuing the treatment of the sequelae of this condition will fall upon the general practitioner in civil practice as well as the physician in the Veterans' Facilities. It is, therefore, the purpose of this paper first to present the clinical picture of the patient with trench foot approximately eight months after the initial exposure and, second, to discuss the results of the various procedures that have been attempted in the later treatment of this condition. In order to evaluate the sequelae, it will be necessary, for comparison, to describe briefly the initial stages also. For the sake of simplicity in presentation, all the cases have been arbitrarily grouped into two categories, namely those without any significant loss of tissue, and those with deep gangrene.

Distinction Between Trench Foot and Other Conditions Resulting From Exposure to Cold.—Trench foot develops in soldiers compelled to remain in foxholes or trenches for a prolonged period of time during which their feet are exposed to a damp environment and to cold not necessarily low enough to freeze tissues. The almost continuous contact of the skin with water adds to the hazard of thermal injury, since as a result there is a facilitated transmission of cold to the tissues as well as an increased rate of loss of body heat. A further factor favoring tissue damage is the reduction of the circulation due to the general muscular inactivity and the cramped position in which the lower extremities through necessity must remain for relatively long intervals. Immersion foot develops in survivors of shipwrecks compelled to keep their feet constantly or intermittently immersed in cold sea water for periods of days or weeks while

Presented in part before the Eighteenth Annual Meeting of the Central Society for Clinical Research, Chicago, Nov. 2, 1945, and before the Medical Conference of the Sixth Service Command, U. S. A., Chicago, Nov. 3, 1945.

Received for publication Dec. 12, 1945.

on rubber rafts or in boats. Again, the environmental temperature often ranges around 33° F. Actually, very little difference exists between this state and trench foot.

In contrast, common frostbite and high altitude frostbite follow actual freezing of tissues by exposure to sub-zero weather. High altitude frostbite develops in members of airplane crews at high altitudes, when exposure takes place either through some failure in the heating unit of the suit, or on even momentary withdrawal of an extremity from a heated glove or boot. In neither this condition nor in common frostbite does the factor of exposure to water or mud play an important role.

CLINICAL OBSERVATIONS

The data in the present report were obtained from a study of 633 patients (616 enlisted men and 17 officers) with varying degrees of trench foot, who came under observation two to thirteen months after exposure to the elements. These men remained under our care for from two to seven months and were then either returned to duty or discharged from the Army.

Patients With One or More Exposures and No Gangrene.—Of the entire series of 633 patients, 596 or 94.2 per cent had one or more distinct exposures without having developed deep gangrene on any occasion. Of this group, 526 had only one attack which was sustained in combat either in Italy in the period from November, 1943, to March, 1944, or in France, Germany, Luxembourg, Holland, or Belgium, between October, 1944, and January, 1945. The duration of exposure varied between three and fifty-four days, with an average of fourteen days. In practically all instances, the environmental temperature was around freezing or slightly above that point, and the patients were exposed to almost continuous rain. For the most part, their feet were immersed in water and mud for a number of days, without the opportunity of changing socks and shoes, except at rare intervals.

Seventy patients had had two or more attacks without developing deep gangrene. Sixty of them were exposed to the elements on two, and 10 of them on three distinct occasions. In the later instances, they sustained either a fresh case of trench foot or an exacerbation of the initial one. In the case of the patients with two attacks, the first exposure was in Italy from November, 1943, to March, 1944. The duration of the exposure was about the same as in the case of the group with a single attack, namely, an average of fifteen days, with a range of from one to sixty days. All of these patients were hospitalized for an average of nine weeks and then sent to convalescent camps or reconditioning centers, from which they were eventually assigned to duty. The second exposure in this group took place in the period between August, 1944, and February, 1945, in France, Germany, or Holland. Again these soldiers were hospitalized, but this time they remained as patients until they reached this hospital.

The 10 individuals with three exposures experienced two of these in Italy, first at Cassino and then at Anzio, and the third in France, Germany, or Holland. Following each of the first two attacks, the patients were returned to duty after

a varying period of hospitalization. With the third exposure, they were hospitalized for the last time, reaching this hospital approximately two months after the acute stage.

Patients With Deep Gangrene and Subsequent Loss of Tissue.—Only 37 patients (5.8 per cent) sustained deep gangrene of the feet with the resulting loss of tissue. This occurred after one exposure either in Italy in the period between November, 1943, and March, 1944, or in France, Germany, Belgium, or Luxembourg, between October, 1944, and January, 1945. The average period of exposure was eight days, with a range of from one to thirty-four days. All of the patients in this group were at complete bed rest when they reached this hospital approximately two to six months after the initial injury.

It is of interest to note that in both patients with and those without deep gangrene no correlation exists between the severity of the condition and the duration of exposure to the elements (Table I). Furthermore, it would appear that the individuals with an old history of frostbite or a previous attack of trench foot are no more liable to develop gangrene than are those exposed only once.

TABLE I. FREQUENCY OF LOSS OF TISSUE IN SERIES OF 633 PATIENTS AND CORRELATION WITH OTHER FACTORS

EXTENT OF PATHOLOGY	NUMBER OF CASES	% ENTIRE SERIES	AVERAGE PERIOD OF EXPOSURE (DAYS)	THOSE WITH PREVIOUS EXPOSURES (% OF GROUP)	THOSE WITH OLD HISTORY OF FROSTBITE (% OF GROUP)
Complete loss of one or both feet	1	0.1	12	0	0
Loss of toes and part of foot, both sides	2	0.3	7	0	0
Loss of toes and part of foot, one side	1	0.1	4	0	0
Entire loss of one or more toes, both feet	3	0.5	6	0	0
Entire loss of one or more toes, one foot	7	1.1	12	0	0
Loss of part of one or more toes or heel	23	3.6	7	0	10
Superficial gangrene, more extensive	33	5.3	9	0	0
Superficial gangrene, mild	15	2.4	6	0	0
No loss of tissue	548	86.6	14	12.8	7.7

Clinical Picture Shortly After Exposure.—The first symptoms experienced by most of the patients in the series were not severe or violent pains, but rather numbness, an aching sensation, intense coldness, and swelling of the feet. In some instances, the soldiers were compelled to seek medical aid after they had removed their shoes and then were unable to replace them because of the swelling. On leaving the foxhole and beginning to walk, a number of men experienced severe pins-and-needles sensations on the plantar surface of the feet.

By the time the soldiers reached a fixed installation, it could generally be determined whether or not they were going to lose any significant quantity of tissue. In those individuals who were fortunate enough to escape without any gangrene or perhaps with only involvement of the superficial layers of the skin, the feet were found to be cold, pale or cyanotic, swollen, and painful. In the

severe cases, swelling and discoloration were marked. In many of these, vesicles were present on the dorsum of the feet, which, in some instances, developed into large painful blisters containing lemon-colored or clear serous fluid. In most individuals desquamation of practically the whole sole was present, and in some this occurred a number of times. Following the loss of dead epidermis, the feet began to perspire. This generally occurred while the patients were still at bed rest, and, although minimal at the beginning, it became marked in many instances. Sweating was most often noted in the foot that was cold and cyanotic, but it was also present when the extremity was warm and of normal color.

As the patients remained in the hospital, only a small number of them demonstrated a transient period of hyperemia, as manifested by marked warmth and redness of the skin of the foot. This response subsequently disappeared and the foot became typically cold and cyanotic. The cyanosis was generally accentuated by dependency. Frequently the patients suffered from severe, burning pain, particularly at night, from which they sought relief by uncovering their feet.

For the most part the patients with deep gangrene demonstrated the same early signs and symptoms except that the clinical picture was of a more severe nature. Marked swelling, cyanosis or pallor, blister formation, severe pain in the feet, and numbness were common findings. In some instances gangrene was already present when the patient reached the Battalion Aid Station, but more often it appeared only after six to ten days of hospitalization. At times the gangrene was preceded by large hemorrhagic blisters. The involved areas quickly became black and mummified. In some individuals ulcerated sites were present; above these the tissues showed signs of inflammation. In others complicating infection already existed.

It is not within the scope of this paper to discuss treatment during the early stage of trench foot. From a review of the records of the patients studied, it is difficult to assay with any degree of accuracy the relative worth of the various measures which had been initiated.

SEQUELAE

Manifestations of the later stage of trench foot, as studied in this hospital, can grossly be divided into three general categories. One group of patients demonstrated signs suggestive of excessive sympathetic activity, but had minimal complaints. Another group had symptoms referable to involvement of peripheral nerves, but showed few objective findings. The patients in the third group displayed both subjective and objective clinical manifestations.

Patients With Predominant Signs of Excessive Sympathetic Activity.—Of the entire group of patients, 144 (22.8 per cent) demonstrated findings which were primarily the result of excessive sympathetic activity. The skin temperature of the toes was found to be low; frequently lower than the environmental temperature. Hyperhidrosis also was present, varying from slightly greater than normal to the point where the sweat rolled off the foot almost in a continuous flow. The quantity of perspiration was definitely increased by emotional

factors. The fact that the skin temperature was lower than the environmental temperature was due to the cooling effect produced by the evaporation of perspiration. Cyanosis of the feet, particularly in the dependent position, was also a prominent finding in this group.

A number of patients would occasionally show a change from a blue, cold foot to a red, hot one. This effect could be produced by exposing the extremities to a warm room or, in some instances, by walking a short distance with shoes on. At other times, for no apparent reason, the foot would become red and hot, and then revert to a cold state. Mottling of the skin was a fairly common finding. In some patients this was only a transient phenomenon, while in others it remained for a relatively long period of time. Various types of patterns were present, occasionally in the same individual. For the most part the mottling was produced by sharply demarcated areas of rubor on a background of cyanosis, interspersed with patches of pallor.

Examination of the large peripheral vessels in the patients with no deep gangrene revealed the absence of the dorsalis pedis artery, either on one side or both, in about 6 per cent of cases (Table II). Whether or not this finding had any significance is difficult to state since comparable results have been noted in groups of normal soldiers. No signs of arteriosclerosis were observed in any of the patients in the series. In the case of the individuals with deep gangrene, the dorsalis pedis artery was not palpable in those instances in which the process had extended onto the dorsum of the foot. Similarly, in one instance, the posterior tibial artery could not be felt. A history of intermittent claudication was obtained only infrequently, thus suggesting that for the most part there was no impairment of the blood supply to the muscles of the legs.

TABLE II. MANIFESTATIONS FOUR TO THIRTEEN MONTHS AFTER EXPOSURE IN A SERIES OF 596 PATIENTS WITHOUT GANGRENE

SIGNS	FREQUENCY %	SYMPTOMS	FREQUENCY %
Cyanosis	59.1	Aching	3.8
Absent pulsations, large arteries	6.0	Tenderness in sole of foot	13.6
Sweating	50.4	Numbness	16.6
Abnormal gait	34.0	Neuritic pains	14.3
Atrophy of muscles	14.7	Hypesthesia	41.5
Stiffness of toes	10.0	Burning and tingling	21.9
Coldness	27.9		
Edema	17.4		

Oscillometric readings were performed on the first 40 patients examined, and no significant alterations were observed. The effect of indirect vasodilatation, brought about by applying hot-water bags to the abdomen and chest and covering the subject with a number of woolen blankets, was studied on 25 subjects. In all instances, this procedure brought the skin temperature, which was low at the beginning, to a level considered to be normal under these circumstances. In 11 cases, a paravertebral lumbar sympathetic block with procaine was done and a similar type of skin temperature response was obtained. With

the rise in the skin temperature, the cyanosis of the foot was replaced by rubor and the hyperhidrosis disappeared entirely for a short period.

In 10 patients with cyanosis but no deep gangrene, the reactive hyperemia test¹ was performed. In all individuals the flush, which appeared on removal of the pressure in the cuff, spread over the leg within five seconds and involved the toes maximally in ten seconds. The flush faded out in about one to two minutes. The rapidity of the response indicated a normal reaction of the cutaneous arterioles and small vessels (capillaries and subpapillary venous plexuses) to a period of anoxia and helped to rule out the presence of occlusive vascular disease in these vessels.

The above tests substantiated the view that the late findings in this group were due primarily to excessive sympathetic activity rather than to organic involvement of the blood vessels of the lower extremities.

Patients With Manifestations Referable to Peripheral Nerve Involvement.—

The second category included 63 patients (9.9 per cent) in whom the signs and symptoms were suggestive primarily of some type of peripheral nerve involvement. Objectively there were frequently very few abnormalities noted. The main complaint was tenderness over the metatarsophalangeal portion of the foot, which at times was of such a degree that the patients did not allow even the slightest pressure to this part. As a result, some of them were unable to walk at all, or, when they did, they placed their weight on the heel or along the lateral edge of the foot. Many of these individuals were found to have areas of hypesthesia to pinprick and cotton wool, which corresponded closely to the sites which were sensitive to deep pressure. The hypesthesia sometimes involved the plantar and even dorsal surfaces of the toes and the dorsum of the foot. Anesthesia was rarely present. In some individuals hyperesthesia was a disturbing symptom. Sensation in the legs was only infrequently altered.

The patients in this group also complained of various types of paresthesias, such as burning and stinging sensation and a pins-and-needles sensation in the toes. Furthermore, they described shooting pains in the feet, which appeared while at rest, and a sensation of numbness in some of the toes.

Patients With Both Syndromes.—The third and largest group consisted of 426 cases (67.3 per cent) showing signs and symptoms of both excessive sympathetic activity and some type of peripheral nerve involvement. Besides these findings, many of the patients in this category, as well as in the other two, entered the hospital still showing the presence of considerable desquamation, thick epidermis on the plantar surfaces of the feet (Fig. 1). This material gradually fell off, leaving new, thin skin. Marked swelling of the toes and, to a less extent, of the feet was present in 28 patients (Fig. 2).

The presence of atrophy of the small muscles of the foot, giving the appearance of an abnormally high arch, was observed to some degree in most of the individuals and was quite marked in 26 patients. It was difficult to determine whether the response was a nonspecific effect due to disuse or whether it was part of the pathology of the trench foot syndrome. However, the existence of histologic alterations in the muscles and nerves in the initial phase of this con-



Fig. 1.—Typical case of hyperkeratosis of the skin three months after exposure to snow and cold, wet weather for three days. Skin wrinkled and fissured, similar to type of response seen after long immersion of tissues in water. Dry gangrene at tips of toes. Normal pulsations in peripheral arteries.

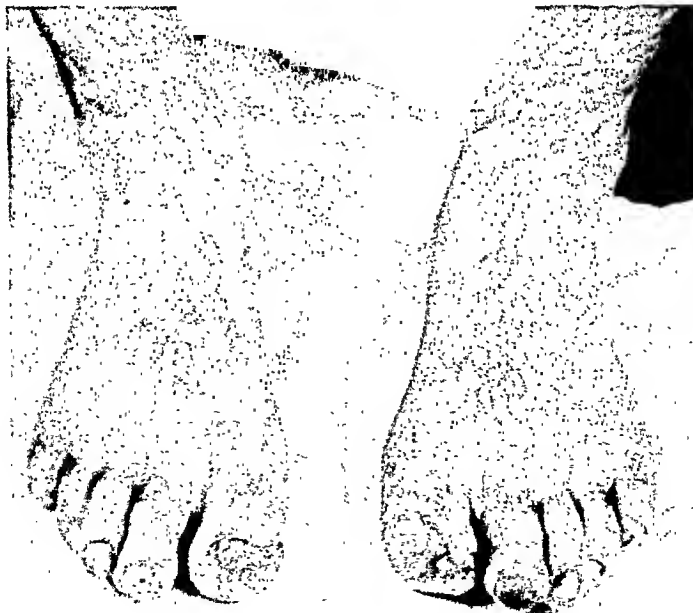


Fig. 2.—Persistent swelling of feet and presence of gangrene four months after exposure to the elements for eight days. Granulating wounds of both great toes present and also some infection.

dition² favors the latter view. In some instances, in spite of an intensive and prolonged program of exercises utilizing the small muscles of the foot, these patients showed no beneficial effects and, at the time of discharge from the hospital, considerable atrophy still existed.

Osteoporosis of the bones of the feet was a fairly common finding in the more severe cases. This may also have been either a response to the long period of inactivity or part of the trench foot syndrome. In several instances, the process was no longer present at the end of the period of hospitalization. More frequently, however, very little change was observed in the final film after two to three months of physical activity. Whether or not this change is ordinarily an irreversible one can only be determined by follow-up studies on such a group.

Among the patients with one or more exposures and no deep gangrene, there were 48 who entered this hospital still showing areas of superficial gangrene. These were generally present on pressure points in contact with the shoe, such as the medial aspects of the feet (Fig. 3, A), the tips of the toes, and occasionally the heels. For the most part, the gangrenous material separated spontaneously, leaving exposed a thin, tightly drawn, smooth, shiny skin which gradually resumed a normal appearance (Fig. 3, B). It is of interest that in a number of these patients the original description of the lesions would have supported the belief that a much more severe type of involvement existed than was substantiated by subsequent events. Such findings are in accord with the view that conservatism should be practiced in the early treatment of gangrene of the feet in trench foot.

Practically none of the patients showed vesicles at this stage of the disease. Frequently one or more toenails had fallen off, leaving the nail bed exposed; or the nails were distorted with a considerable amount of debris beneath them. Dermatophytosis was a common finding in this group.

Forty-two of the patients demonstrated marked stiffness of the toes with a shiny, firmly attached skin. In some individuals, the great toe was widely separated from the others (Fig. 4) and was either hyperextended (in the form of a pseudo Babinski sign) or flexed. These observations have been previously described by other investigators.³ There was no correlation between the degree of stiffness and the severity of the condition originally, and it was felt that this response was probably due in great part to disuse.

With regard to the group of 37 patients with deep and extensive gangrene, frequently the gangrenous portions were partially separated at the line of demarcation at the time of admission to the hospital. The lesion was generally bathed in foul-smelling pus and in some instances there was evidence of extensive infection throughout the gangrenous portions. On numerous occasions, where the gangrene appeared to be of a dry type, removal of this material through the line of demarcation disclosed a pool of pus beneath it.

Infection was invariably a mixed one and very commonly penicillin- and sulfonamide-resistant *Bacillus proteus* and *Bacillus pyocyaneus* were present. There was little spread of the infection to the adjacent soft tissues, but osteomyelitis was frequently noted in the proximal stump.

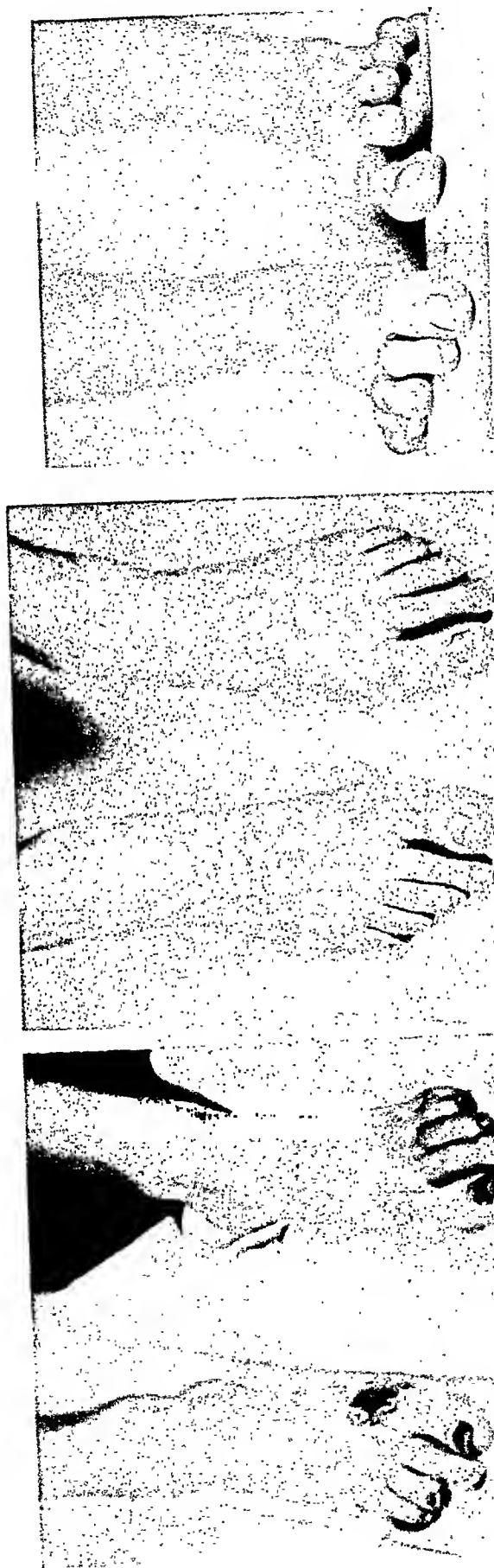


Fig. 4.

B.

Fig. 3.

A.

Fig. 3.—A, Superficial gangrene on medial aspect of right foot and some deep gangrene at tips of toes still present two months after exposure. B, Two months later. Superficial gangrenous area completely healed, leaving only some pigment deposits in involved site. Loss of nails on a number of toes.

Fig. 1.—Characteristic position of great toe of left foot and stiffness of toes nine months after onset of condition.

LATER THERAPY

Most of the patients with trench foot arriving at this hospital had been at complete bed rest without latrine privileges for from one to twenty weeks, with an average of nine weeks. Therefore, the treatment, whenever possible, was directed at making them ambulatory as rapidly as their condition permitted. The problem of reconditioning was made more difficult by the fact that many of the men still had considerable tenderness of the soles of the feet, pain, and swelling. All these factors made the resumption of walking an unpleasant experience. Therapy, therefore, was divided into two periods, namely, the medical and surgical treatment, followed by the reconditioning program.

MEDICAL AND SURGICAL TREATMENT

Massage and Removal of Dead Epidermis.—Most of the patients showed the presence of a considerable amount of desquamating epidermis (Fig. 1), which was removed by rubbing lanolin ointment, containing 4 per cent salicylic acid, into the skin. The procedure was performed by the patient at frequent and scheduled intervals during the day, under the supervision of a physical therapist. When desquamation was completed, the ointment was replaced by mineral oil and a dilute solution of alcohol for the purpose of massage. This step was carried out at least twice daily for half-hour intervals either by the patient himself or by the patient in the next bed. Considerable emphasis was also placed on the practice of active manipulation of the toes in order to counteract the stiffness, contractures, and atrophy of disuse. In some instances where these findings were quite marked, the daily routine of massage was supplemented by passive and active exercise of the toes by the physical therapist.

Typhoid Vaccine.—When patients with trench foot were first received at this hospital, an attempt was made to determine the effect of typhoid vaccine on the condition. A number of subjects picked at random were given this treatment; after a series of 10 to 15 intravenous injections every other day, the results were analyzed. Preliminary testings were done on each patient and the dosage of the vaccine was increased to the point where a single injection was followed by a rise in body temperature to approximately 102° F.

For the most part, this treatment brought about no definite change in the clinical picture, except for a significant reduction in the swelling of the feet in some instances. Typhoid vaccine was, therefore, subsequently utilized only in those patients in whom edema was the main complaint. In 10 of 16 individuals, there was a rapid subsidence of the swelling after the first or second administration, and the therapeutic effect continued but was less marked with the following 10 to 12 injections. At the end of the period, all of these patients were fully ambulatory, whereas previously they had been compelled to lie in bed a considerable portion of the day because of the swelling. It is of interest that complete bed rest for a number of weeks before this treatment had been started had produced little change in the edema. In the remaining six patients, typhoid vaccine did not have any therapeutic effect.

It would appear, therefore, that this treatment has some promise and that it should at least be tried in the case of every patient with trench foot who has appreciable swelling of the feet. Whether or not it will have any effect can be readily determined after the second or third injection.

Orthopedic Appliances.—As soon as the patient without gangrene was physically able, he got out of bed and began to walk, using low shoes. It was felt that these would be more satisfactory than the garrison shoes because of their light weight and because less of the foot was covered, thus permitting greater evaporation of perspiration. In patients in whom hyperhidrosis was a prominent symptom, the shoes were perforated in a number of sites, to facilitate removal of the excessive perspiration by air currents.

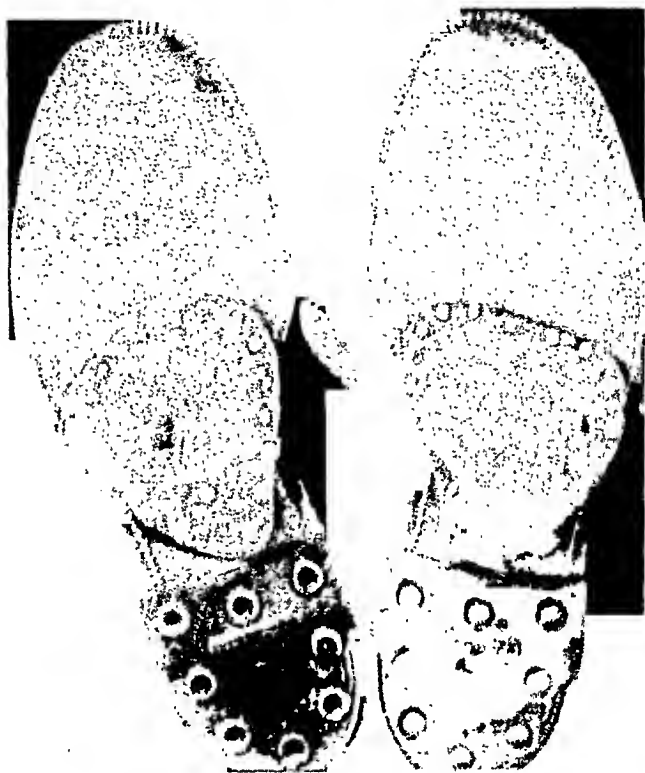


Fig. 5.—Application of anterior heel in front of normal heel, to remove pressure from sole of foot.

At least 182 of the patients without gangrene complained of tenderness over the distal portion of the foot on the plantar surface. In an attempt to protect this area from the weight of the body, these individuals, on walking, shifted the pressure to the heel or to the lateral edge of the foot. In order to counteract these unnatural gaits, with their resulting undesirable alterations in the dynamics of the foot and spine, a rubber heel or a thick piece of leather was attached to the under surface of the shoe in front of the ordinary heel* (Fig. 5). The patient then walked on the two heels, thus applying practically no pressure to the sole of the shoe which covered the sensitive portion of the foot. As he continued to walk, the anterior heel which received most of the friction

*The authors are indebted to Captain R. Buck at whose suggestion this procedure was given a clinical trial.

gradually wore down, until eventually the pressure was again applied to the sole of the shoe. In most instances, the sensitivity of the foot to pressure was lost or diminished by this time and the heel was removed.

Formalin by Iontophoresis.—Since hyperhidrosis was a common and, at times, incapacitating complaint, attempts were made to treat it, generally without too much success. Low shoes, daily foot baths, foot powders, and frequent changes of socks only partially counteracted this condition.

At the suggestion of Freis,⁴ patients with severe hyperhidrosis were treated with formalin by iontophoresis. The use of formalin baths for hyperhidrosis has been a fairly common therapeutic procedure in the field of dermatology and it was felt that this action could be accentuated by forcing the formalin into the skin by means of a galvanic current. A description of the procedure we used to accomplish this follows.

An ordinary galvanic current machine was connected to the patient by placing a large negative electrode in close contact with the abdomen, while the positive electrode was immersed in a bakelite container filled with 1 per cent formalin. The patient placed both feet in the basin, which was filled with sufficient solution to reach above the ankles. Ten to 12 milliamperes of current were applied for twenty minutes. A series of treatments consisted of six daily administrations.

In all instances the patients were first skin tested for formalin sensitivity. No patient who showed even the slightest reaction was given this treatment. The presence of sensitivity to formalin appears to be fairly common, as indicated by the finding that approximately 28 per cent of all the individuals tested showed a positive reaction.

Results with formalin by iontophoresis were rather variable. The therapy was begun on 121 patients, but in 29 instances it had to be discontinued after the second or third treatment because of the appearance of a mild dermatitis or fissuring of the skin between the toes. Of the remaining 92 patients, 74 finished one series of six treatments, while 18 were given two series, with an average of thirty-nine days between treatments. In the case of the patients given one series of treatments, 37 showed an almost immediate cessation of sweating, 21 had a fair response, and 16 demonstrated no benefits from the therapy. The patients were re-examined at the end of a four-week period, and, at that time, it was felt that in seven the therapeutic effect was excellent, in 32, good, in 16, fair, and in 19, poor.

Eighteen patients were given a second series of treatments either because no therapeutic effect was noted initially or because the reduction or cessation in sweating was only temporary. In this group, the second series produced a good result in six, a fair response in eight, and a poor result in four patients.

All of the patients discussed were seen at intervals during the subsequent two months, and it was noted that in the great majority of them hyperhidrosis was returning, but generally not to the same degree as previously. The therapy evidently has a definite but transient effect on reducing sweating of the feet in trench foot.

Lumbar Sympathectomy (Table III).—Since vasoconstriction is one of the fundamental factors in the pathogenesis of trench foot and also one of the most constant sequelae, the use of sympathectomy as a possible therapeutic aid has been proposed and has received some clinical trial. This procedure was therefore utilized in a number of individuals in this series.* In nine patients the operation was done primarily for cold sensitivity or excessive hyperhidrosis, with the result that the feet became warm, dry, and normal in color. In two instances in which maceration of the skin and infection had been present, these findings cleared up shortly after sympathectomy. In all nine patients the abnormal response to cold and the associated discomfort were also minimized.

In 10 individuals in whom sympathectomy was performed primarily because of pain on weight bearing, the results were variable. Two patients with pain both in the metatarsal region and in the heels experienced complete relief in the latter site only, while those with symptoms in the metatarsal region alone were for the most part not benefited by the procedure. Somewhat similar results have been reported by Edwards, Shapiro, and Ruffin.⁶ Sympathectomy was also used in a group of patients with deep gangrene, and the results in this type of case will be discussed in the section following.



Fig. 6.—A, Deep gangrene of toes of both feet two months after exposure to snow and cold, wet weather for six days. Areas of dry gangrene demarcated from normal tissue. Foul-smelling discharge present from these sites. Normal oscillometric readings and normal pulsations in large arteries of feet. B, Complete healing two months later, following sympathectomy, amputation of gangrenous toes and, subsequently, pedicle transfer grafts.

Treatment of Extremities With Deep Gangrene.—In only one of the patients with deep gangrene had any surgical procedure been performed before admission to our hospital. In all others, steps had to be carried out to remove the gangrenous material (Fig. 6). In order to facilitate healing, sympathectomy was performed as a preliminary step in 30 patients; in eight of these, the procedure was done bilaterally (Fig. 6). Frequently, removal of gangrenous material and portions of toes was carried out at the same time. Twenty-nine

*A detailed analysis of the efficacy and limitations of sympathectomy has been reported in a separate paper.²

TABLE III. INDICATIONS FOR USE OF LUMBAR SYMPATHECTOMY

CONDITION	RESULTS	REMARKS
Hyperhidrosis alone	Complete cessation of sweating	Operation generally not indicated for this state alone
Hyperhidrosis with maceration of skin and secondary infection	Complete cessation of sweating with healing of skin	Operation definitely indicated
Marked cyanosis and coldness and abnormal response to low environmental temperature	Return of normal color and skin temperature	Operation indicated in some instances
Tenderness of sole of foot on walking	Only occasionally effective	Operation not performed for this condition alone
Neuritic manifestations	Only occasionally effective	Operation not performed for this condition alone
Deep gangrene requiring amputation and skin graft	Aids in healing	Necessary preliminary step in many cases



Fig. 7.—Marked gangrene involving entire foot bilaterally, one month after exposure to snow and cold, wet weather for thirteen days. Both feet subsequently amputated.

amputations were performed, and in each instance conservatism with regard to the amount of tissue removed was practiced. Nine patients required split-thickness skin grafts. In two cases, in which ends of metatarsal bones were exposed with large skin defects, it was necessary to utilize pedicle transfer grafts from the opposite lower extremity in order to obtain well-padded, full-thickness skin (Fig. 6, B). One patient with gangrene of both feet was sent to an amputation center for further treatment (Fig. 7).

When the patients became ambulatory again, they were fitted with special shoes to help overcome the difficulty produced by loss of tissues of the foot. In most individuals in this group, however, very little was required since a useful foot remained.

With respect to the evaluation of sympathectomy in the treatment of gangrene, it must be pointed out that no control series of cases was run simultaneously. Hence, there is no unequivocal evidence that the rate of healing was affected by the procedure. Nevertheless, there was some indication that the increase in circulation which followed had a beneficial effect in those instances in which marked vasospasm was present.

With regard to the use of split-thickness skin grafts and transfer pedicle grafts, there is little question that these procedures definitely reduced the period of invalidism. Furthermore, as a result, a thick layer of skin which responded well to the application of pressure and friction now covered the stump (Fig. 6. B) instead of the usual thin, poorly nourished skin which would have followed as a natural course.*

Therapeutic Procedures of Questionable Value.—A certain number of therapeutic procedures were attempted with little hope that they would prove efficacious. As anticipated, the results were for the most part unsatisfactory. However, the data will be presented, so as to discourage further clinical trials of these medications by other workers.

Four patients with marked signs of excessive sympathetic tonus were given a series of six daily treatments with mecholyl (acetyl-beta-methyl-choline chloride) by iontophoresis. The procedure was similar to that used in the case of formalin by iontophoresis (discussed previously), except that a 0.2 per cent aqueous solution of mecholyl was utilized instead of formalin. It was felt that since mecholyl by iontophoresis is a good local vasodilating agent,⁷ the procedure might help in counteracting the vasospasm which existed in the patients in this group. In each instance the feet became warm for a short period following the treatment, but then reverted to the previous cold, blue state. At the end of the series of treatments, no permanent effect on the condition of the blood vessels was noted in any of the patients and the method was therefore discontinued.

In 11 patients with predominantly peripheral nerve involvement, the effect of large doses of thiamine chloride administered intravenously was studied. Each patient was given 100 mg. of the drug daily for an average of two weeks. No untoward effects were noted following the treatment, and similarly no alteration in symptoms occurred. The patients continued to complain of paresthesias, aching and burning, and sensitivity in the soles of the feet. No data were obtained from the study which would suggest that this type of therapy was at all worth while in the treatment of the neuritic complaints present in the later stage of trench foot.

The effect of Buerger's exercises and Sanders' bed was studied in eight patients with moderately severe trench foot but no gangrene. No obvious alteration was noted in such signs as cyanosis, coldness, or hyperhidrosis; nor was there any reduction in the severity of the symptoms.

In 11 patients, paravertebral lumbar sympathetic blocks were performed. As mentioned previously, this was carried out to determine whether or not the cyanosis, coldness, and hyperhidrosis were due to excessive sympathetic tone. At the same time, an opportunity was afforded to study the therapeutic effect of such a procedure. In five instances, the symptoms were unchanged. The tenderness over the sole of the foot, the swelling, and the neuritic pains were not affected. However, in the remaining six patients, some alleviation of the sensitivity of the sole of the foot resulted, but this lasted for only a short period

*A detailed analysis of the surgical management of gangrene in trench foot will be reported in a separate publication.

of time. It is of interest that, when a number of these were subsequently sympathectomized, the therapeutic effect was much less than anticipated on the basis of the findings following the block.

RECONDITIONING PROGRAM

A number of patients with trench foot did not immediately become ambulatory on reaching the hospital either because of the presence of gangrene or infection or because there was marked sensitivity of the soles of the feet which did not permit weight bearing. A special type of reconditioning program was therefore instituted to take care of these individuals during the period that they were compelled to remain in bed in order to prepare them for the time when they could participate in more active physical exercise. The routine consisted of morning corrective exercise in bed and afternoon sessions of games, tournaments, and various types of physical fitness testing.

As soon as the patients were able to walk around the ward without too much difficulty, they were started on an ambulatory reconditioning program which for the first four weeks consisted of exercises requiring them to be on their feet only a small portion of the time. During the second four-week period, this was gradually increased until the desired level of activity was reached. Then it was maintained for varying periods of time ranging from another month to three months, depending upon the rate of progress of the individual patient.

The men were given various types of rather strenuous calisthenics in a pool, since it was felt that under these circumstances the buoyancy of the water would permit more vigorous use of the muscles of the feet with less associated pain and would also help in the recovery of a sense of balance. Except for an occasional individual who responded poorly to immersion of the feet in water, the men participating in this part of the program appeared to benefit from the exercises.

At the same time, the patients were encouraged to ride a bicycle since this sport helped to improve the tone and the strength of muscles of the lower extremities. Group walking at a leisurely pace was also an important part of the program. The distance covered was gradually increased until it consisted of from 1 to 2 miles. The main purpose was to accelerate the rate at which toughening of the skin on the soles of the feet was taking place.

Results With Reconditioning Program.—The first therapeutic effect from the reconditioning program was a rapid change in the mental outlook of the trench foot patient. Having led a life which was very similar to that of a bed-ridden invalid for the previous two to three months, he suddenly found himself part of a program of gradually increasing physical activity. He began to do things which he did not believe he would ever be capable of performing again, and gradually, as his general physical condition improved, his self-confidence also returned. Constant participation in competitive sports helped change his attitude toward future duties and responsibilities.

When it was felt that the patient with trench foot had obtained maximal benefit from reconditioning with respect to his general health, and that his feet were sufficiently recovered to allow taking part in a fairly normal program of daily physical activity, hospitalization was terminated.

FINDINGS AT FINAL EXAMINATION

Except for 51 men who were transferred to convalescent centers or to other hospitals, the patients were sent either to a limited type of duty or were discharged to civilian life. The factors which were taken into consideration before a decision was reached were the severity of the signs and symptoms that still persisted, the rate of progress of the case in the hospital, the period of total hospitalization, the mental outlook of the patient, and the presence of multiple defects. Among the signs and symptoms, the ones that were given special attention were: the type of gait, the degree of hyperhidrosis, the presence of atrophy of the small muscles of the feet, the actual loss of tissue as a result of gangrene, the distance the patient was able to walk without difficulty, the tendency toward blister formation and fissures, the state of the skin on the soles of the feet, and such complaints as paresthesias and tenderness of the soles of the feet.

Patients Returned to Duty.—In the case of the group returned to duty (33 per cent of the series), most of the men were able to walk without difficulty for at least a mile and they all had a normal gait, placing the pressure properly on the entire foot. They were also able to stand on the distal part of their feet and elevate the heels from the ground. There were no signs of excessive sweating, coldness, atrophy of the small muscles of the feet, or stiffness of the toes. Cyanosis was minimal. There were very few complaints of paresthesias, numbness of the toes, or tenderness of the soles of the feet on walking. These patients had no other medical or surgical conditions, including any type of wound with residuals. During their period of hospitalization, they had shown fairly rapid progress.

Patients Discharged to Civilian Life.—In the case of the patients discharged from the hospital to civilian life (67 per cent of the series), approximately one-third had an associated condition or conditions which by themselves might not have been disabling, but together with a moderate degree of trench foot were sufficient to necessitate discharge from the Army. These medical defects consisted chiefly of a mild-to-moderate degree of psychoneurosis, plantar warts, various orthopedic conditions of the feet, and partially disabling wounds of the lower extremities.

In most instances, these patients did not have a normal gait even after four to eight months following their initial exposure. They either walked on their heels, on the lateral edges of the feet, or kept the toes extended so that they did not participate in weight bearing or propulsion. All of them complained of the inability to walk more than $\frac{1}{2}$ mile without developing severe aching and burning in the feet. Many of the patients still demonstrated an annoying hyperhidrosis, which required changing socks as often as two or three times a day, and other findings indicating excessive sympathetic activity, such as cold, cyanotic feet. Exaggeration of symptoms, particularly in the case of sweating and swelling of the feet, was frequently noted during hot weather. Some of the patients described a neuritic type of pain at rest and also numbness of one

or more toes. Occasionally hypesthesia on the plantar surfaces of the toes and adjoining portion of the foot was still present. For the most part, the skin on the sole of the foot was delicate, probably because the patients in this group walked very little, in order to minimize the associated pain.

Except for two patients with minor lesions and good recovery and one who was transferred to an amputation center, all others with a history of deep gangrene and subsequent loss of tissue were also included in this group. Most of them had experienced a severe attack of trench foot and at the time of their disposition still displayed such sequelae as hyperhidrosis, extreme coldness and cyanosis of the feet, and manifestations of definite neuritic involvement, besides the loss of toes or portions of the feet.

FOLLOW-UP STUDIES

Recently a questionnaire was sent to the first 250 patients in the group returned to civilian life for the purpose of obtaining information concerning their progress in the interval. One hundred eighty-eight replies were received, and the data have been analyzed. It is intended to continue this study at three- to six-month periods in order to determine the residuals of trench foot which persist, and whether or not individuals with this condition become useful members of their community again.

From an examination of the questionnaires, it was found that 68.3 per cent of the patients obtained jobs within an average of 4.2 weeks after being discharged from the Army. Four per cent enrolled for courses in technical schools and colleges, while 27.7 per cent had no job at the time of filling out the questionnaire (approximately two and one-half months after they had left the hospital). Forty-nine per cent of those who were working still had the job they originally obtained. Thirty-two per cent of the entire group, including those without jobs at present, had to change positions from one to three times. As will be noted in Table IV, A, a great proportion of the men had jobs requiring physical labor, while only a small number were doing a sedentary type of work. For the group as a whole, the men spent an average of four hours on their

TABLE IV. EVALUATION OF PROGRESS OF PATIENTS APPROXIMATELY THREE MONTHS AFTER RETURN TO CIVILIAN LIFE

<i>A. Types of Occupation</i>			
TYPE	% OF CASES	TYPE	% OF CASES
Farming and gardening	15.4	Factory worker	30.5
Cab or truck driving	14.6	White-collar job	24.0
Machinist or helper	15.5		
<i>B. Symptoms Which Persist in the Feet</i>			
SYMPTOMS	% OF CASES	SYMPTOMS	% OF CASES
Burning sensation	72	Tenderness, sole of foot	69
Hyperhidrosis	63	Dermatophytosis	28
Blister formation	26	Swelling	59
<i>C. Ability to Walk</i>			
DISTANCE	% OF CASES	DISTANCE	% OF CASES
Less than $\frac{1}{4}$ mile	12.9	$\frac{3}{4}$ mile	8.7
$\frac{1}{4}$ mile	12.1	1 to $1\frac{1}{2}$ miles	33.7
$\frac{1}{2}$ mile	17.2	2 to 3 miles	15.4

feet daily. Twenty-two per cent of them were able to do their job as well as the man working next to them who had no physical disability, while 78 per cent were not.

With respect to their medical status, a great proportion of the patients still had numerous complaints (Table IV, *B*). Their ability to walk ranged from less than $\frac{1}{4}$ mile to as much as 2 or 3 miles (Table IV, *C*). Forty-seven per cent of the patients stated that they had observed no improvement in their condition since they had left the hospital, 43 per cent noted slight improvement, and 10 per cent noted more marked improvement.

SUMMARY AND CONCLUSIONS

1. The later sequelae of trench foot were studied in a series of 633 soldiers with varying degrees of involvement of the feet.

2. Ninety-four and two-tenths per cent of the patients had one or more exposures but never developed gangrene.

3. Five and eight-tenths per cent of the patients developed gangrene with the loss of deep tissues of the feet.

4. No apparent correlation could be obtained between the duration of the initial exposure and the severity and persistence of the condition. Similarly, there was no tendency for the patients with a history of frostbite to develop a more severe case of trench foot.

5. Shortly after exposure, the feet were swollen and discolored and showed vesicle formation, desquamation of the sole, and hyperhidrosis. Such complaints as pain, numbness, and paresthesias were frequently present.

6. The sequelae of trench foot were divided into three groups, of which one demonstrated findings indicating excessive sympathetic activity, the second, a clinical picture suggestive of some type of peripheral nerve involvement, and the third, signs and symptoms common to both of the other two groups.

7. Various tests were performed on the group of patients with signs of excessive sympathetic activity but without gangrene. These procedures supported the view that no occlusive vascular disease was present in the later stage of uncomplicated trench foot.

8. Frequently, no correlation could be made between objective findings and complaints experienced by the patient. In some cases, practically no signs of excessive vasomotor tonus were present, and the feet looked normal on inspection: still the patients walked on their heels or along the lateral borders of their feet, because of tenderness in the soles. They also had various types of paresthesias. On the other hand, some individuals showed signs of excessive sympathetic activity, such as cold, wet, cyanotic feet, or they even had superficial gangrene, without any indication of nerve involvement. Their gait was normal; many of them were able to walk a mile or two without experiencing any discomfort.

9. The treatment of the sequelae of trench foot was divided into two categories, namely, medical and surgical therapy and the reconditioning program. The medical and surgical treatment was directed toward removal of the dead

epidermis, counteracting the stiffness of the toes and atrophy of the small muscles of the feet, reducing the hyperhidrosis, minimizing the pressure applied to the tender soles of the feet on walking, and decreasing the swelling.

If amputation was necessary, conservatism was practiced, and every effort was made to control infection. When large skin defects existed or when skin was lost on weight-bearing surfaces, various types of skin grafting were found to be helpful. Sympathectomy appeared to have a definite place in the treatment of only certain selected cases; in the majority of instances it was not indicated.

10. The purpose of the reconditioning program was to build up the general physical condition of the patient first and then to concentrate on the feet. The skin of the feet was hardened by such procedures as calisthenics in the pool and gymnasium, walking, and bicycling. At the same time, the small muscles of the feet were exercised in order to counteract the atrophy.

11. After the completion of the reconditioning program, 33 per cent of the series were returned to a limited type of duty. Most of the men in this group had a normal gait, were able to walk a mile or more, had no signs of hyperhidrosis, atrophy of muscles of the feet, or stiffness of the toes. Symptoms indicating nerve involvement were minimal, the mental outlook of the patients was satisfactory, and they did not have other medical or surgical defects.

Sixty-seven per cent of the series were discharged to civilian life. Most of the men in this group demonstrated signs of excessive sympathetic activity, walked poorly and only for short distances, complained of various types of paresthesias, or had lost portions of their toes and feet as a result of gangrene.

12. In conclusion, it is obvious from this study that trench foot is associated with a long period of at least partial physical incapacitation. The exact duration of this interval can only be determined by follow-up studies. In view of the fact that the sequelae of trench foot are aggravated by extremes of environmental temperatures, patients with this condition should, whenever possible, live in a place where a moderate climate exists most of the year.

The authors wish to express their appreciation to the many medical officers in overseas medical units, who first treated the patients in this series, and to the various ward officers at the Mayo General Hospital, and among them, particularly, Captains H. H. Lampert, R. H. Smith, P. B. Olsson, and R. Murray, who have helped generously in the study. They are also indebted to T/4 Adolph Schwartz and Cpl. Jacob W. Fite for their valuable assistance in the compilation of the data which form the basis for this report.

REFERENCES

1. Pickering, G. W.: On the Clinical Recognition of Structural Diseases of Peripheral Vessels, *Brit. M. J.* 2: 1106, 1933.
2. Friedman, N. B.: The Pathology of Trench Foot, *Am. J. Path.* 21: 387, 1945.
3. Patterson, R. H., and Anderson, F. M.: War Casualties From Prolonged Exposure to Wet and Cold, *Surg., Gynec. & Obst.* 80: 1, 1945.
4. Freis, E. D.: Personal communication.
5. Shumacker, H. B., Jr., and Abramson, D. I.: Sympathectomy in Trench Foot, *Ann. Surg.* (In press.)
6. Edwards, J. C., Shapiro, M. A., and Ruffin, J. B.: Trench Foot, Report of 351 Cases, *Bull. U. S. Army M. Dept.* 83: 58, 1944.
7. Abramson, D. I., Pierst, S. M., and Flachs, K.: Evaluation of Local Vasodilator Effects of Acetyl-beta-methylcholine Chloride (Mechoyl) by Iontophoresis, *AM. HEART J.* 23: 817, 1942.

THE CONSTRUCTION OF THE CARDIAC VECTOR

R. F. HILL, M.S., M.A.*
NEW ORLEANS, LA.

A CERTAIN problem in connection with the construction of the cardiac vector representing the "manifest potential" has recently come to our attention.¹ Inasmuch as this problem may be a source of trouble and misunderstanding to other workers, and since it involves concepts which perhaps need further clarification, we shall discuss it in some detail.

The problem can be illustrated best by an example. Suppose the values of the potential at the right arm, left arm, and left leg are measured either by Wilson's common terminal technique² or by Goldberger's augmented-potential method,³ and suppose we find that:

$$\begin{aligned}V_R &= -3 \\V_L &= +10 \\V_F &= -7.\end{aligned}$$

Then if we either measure the limb lead potential differences simultaneously or obtain them from the unipotential values, we would find, of course, that:

$$\begin{aligned}e_1 &= +13 \\e_2 &= -4 \\e_3 &= -17.\end{aligned}$$

Now let us construct the cardiac vector, using both sets of values, and let us call the construction using e_1 , e_2 , and e_3 Method I, and the construction using V_R , V_L , and V_F Method II.

Method I, following Bayley's notation,⁴ is shown in Fig. 1. The three axes, representing the three limb lead directions, make angles of 60° with each other. Calling the cardiac vector E , we find that it has a magnitude of 17.8 units and makes an angle of 42° with the horizontal.

Method II makes use of the triaxial system formed by OR , OL , and OF in Einthoven's triangle (Fig. 2). O is the center of the triangle, at which the tail of the cardiac vector is located, and constitutes the origin of this second system. The new axes also make angles of 60° with each other, although they do not have the same directions as those of Method I. Actually, the second triaxial system consists of a rotation of the first through an angle of 30° . Using the

*From the Department of Physiology, Louisiana State University School of Medicine, New Orleans, La.

Received for publication Aug. 25, 1945.

*Now in the Physics Department, Memorial Hospital, New York, N. Y.

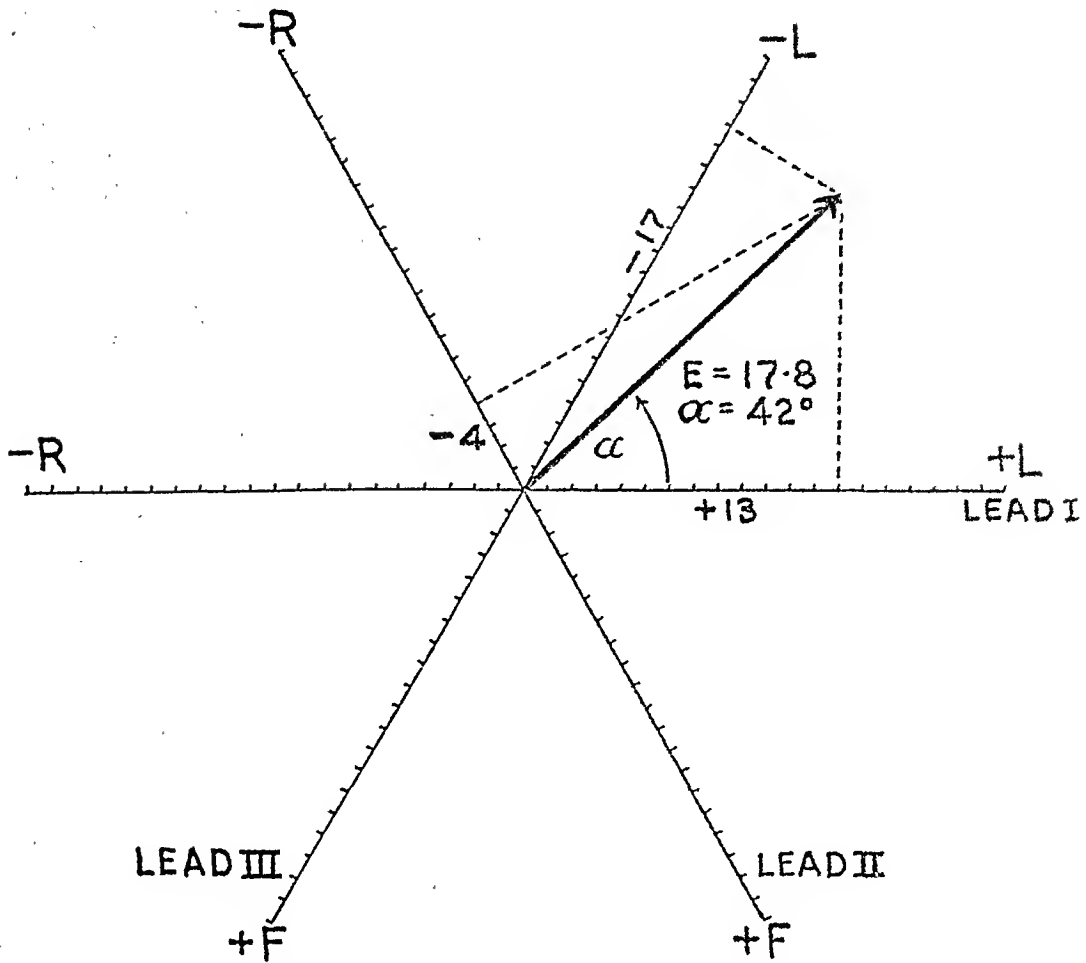


Fig. 1.—Construction of E by Method I. $c_1 = +13$, $c_2 = -4$, $c_3 = -17$. E is seen to be 17.8 units and $\alpha = 42^\circ$.

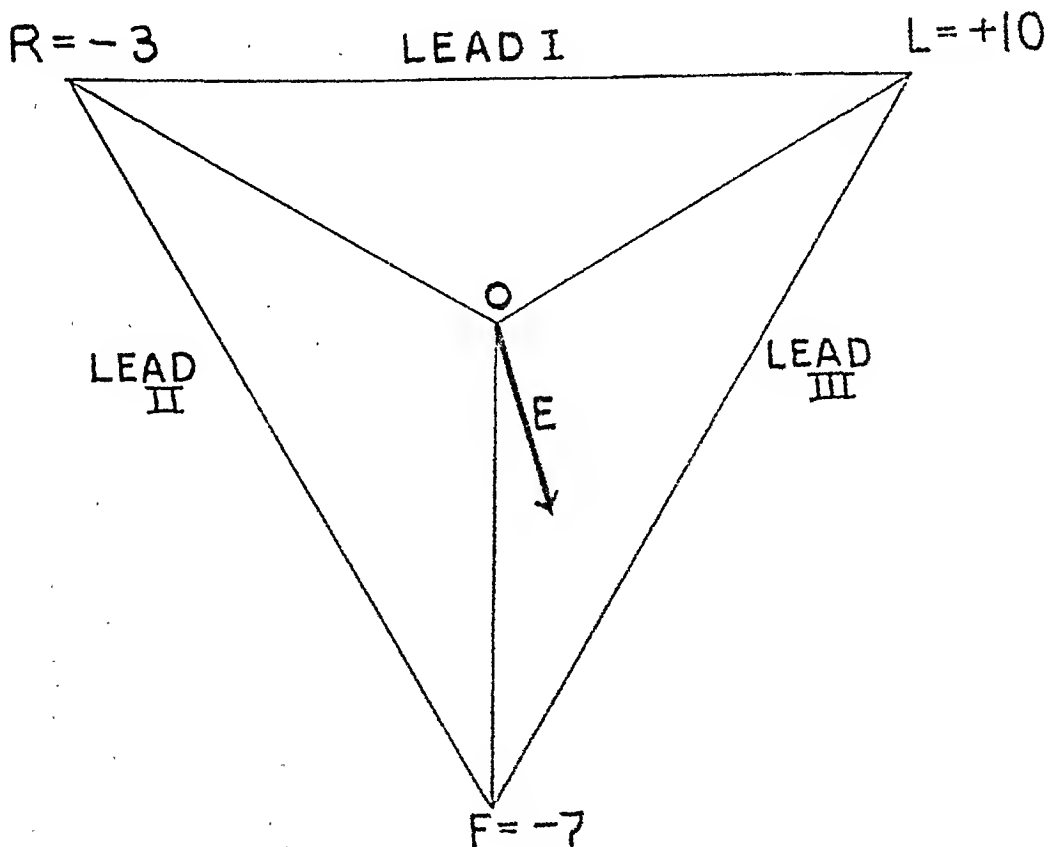


Fig. 2.—Einthoven's triangle.

values of V_R , V_L , and V_F given previously, we construct as in Method I. Fig. 3 shows the vector constructed by Method II. This time the resultant vector has a magnitude of 10.2 units, although it still makes an angle of 42° with the horizontal. Therefore, the result obtained by Method I is 17.8 units, which is $\sqrt{3}$ times higher than the result obtained by Method II, 10.2 units.

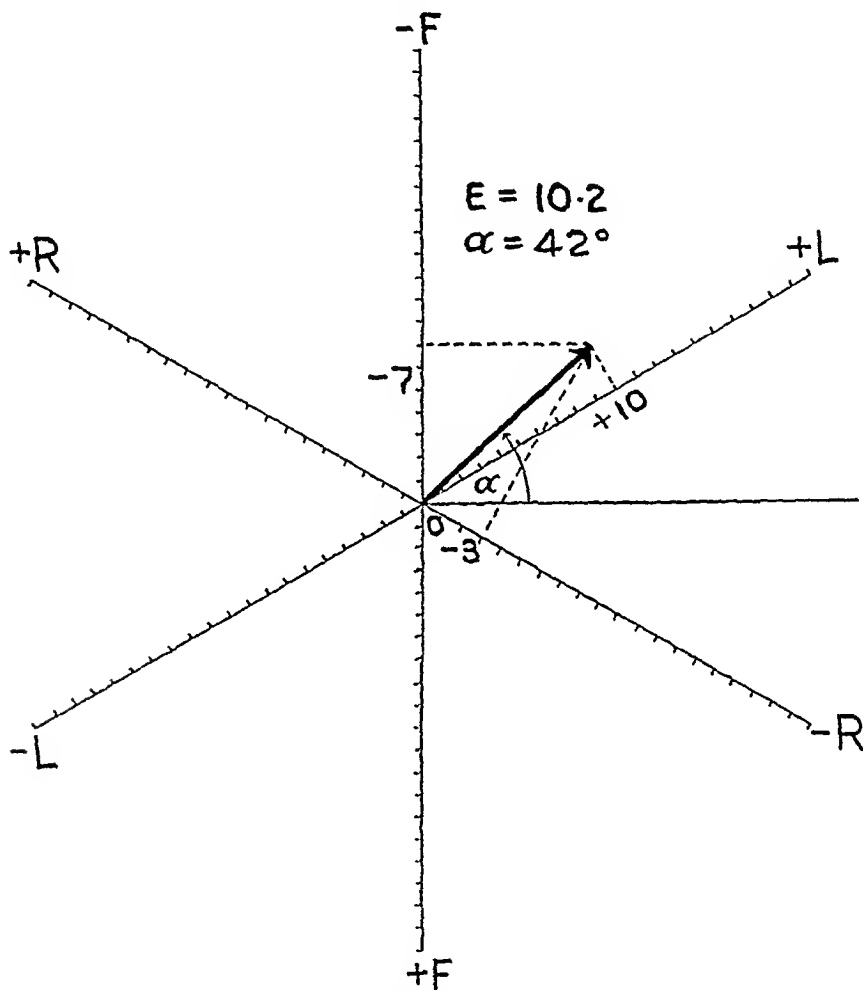


Fig. 3.—Construction of E by Method II. $V_R = -3$, $V_L = +10$, $V_F = -7$. E is now 10.2 units, while α is still 42° .

To illustrate further, let us suppose that we actually know in advance the magnitude and direction of E. To simplify the calculation, let E be 17.8 units and let it make an angle of 42° with the horizontal (Lead I). Then by reversing the procedure of Method I, we obtain

$$\begin{aligned} c_1 &= -13 \\ c_2 &= -4 \\ c_3 &= -17. \end{aligned}$$

The values of V_R , V_L , and V_F , obtained in a similar manner by reversing the procedure of Method II, are

$$\begin{aligned} V_L &= +17.4 \\ V_R &= -5.3 \\ V_F &= -12.1. \end{aligned}$$

This is shown in Fig. 4. From these values, we see that

$$e_1 = +22.7$$

$$e_2 = -6.8$$

$$e_3 = -29.5.$$

Evidently these values of e_1 , e_2 , and e_3 are $\sqrt{3}$ times higher than the values obtained by the direct projection of E on Leads I, II, and III, or, what amounts to the same thing, V_R , V_L , and V_F are $\sqrt{3}$ times higher than the originals.

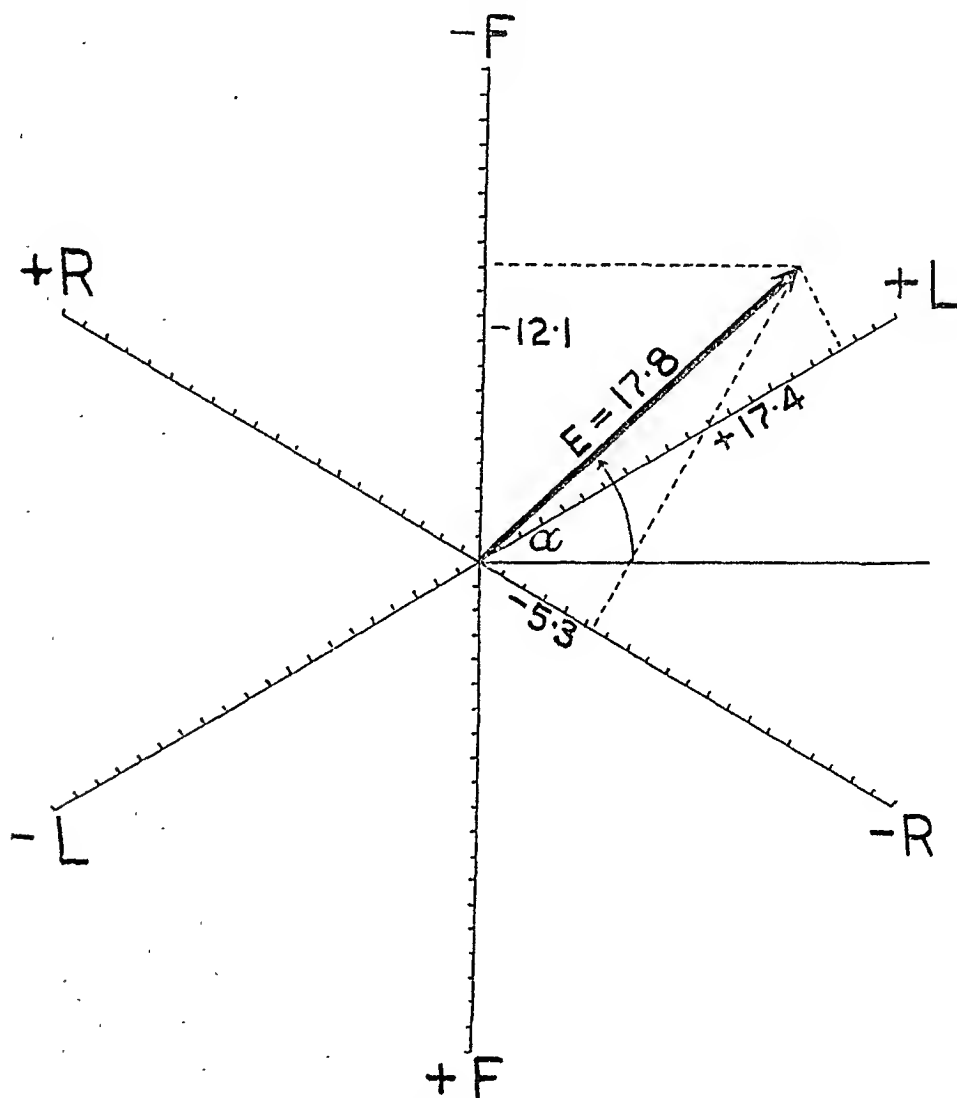


Fig. 4.—Resolution of E to find V_L , V_R , and V_F . E is assumed to be 17.8 units, and α is 42° . We find that $V_L = +17.4$, $V_R = -5.3$, $V_F = -12.1$.

To summarize: the cardiac vector as obtained by Method I is $\sqrt{3}$ times *higher* than the cardiac vector obtained by Method II. On the other hand, if we start with a given value of E , then the values of e_1 , e_2 and e_3 obtained by direct projection onto the limb leads turn out to be $\sqrt{3}$ times *lower* than the values obtained by finding V_R , V_L , and V_F , followed by the necessary subtractions.

It is natural to ask which method is correct. The answer is "both." In order to explain this apparent discrepancy, we shall have to investigate the nature of what we are doing when we make these constructions. The present

paper is an attempt to clarify some misconceptions which appear to be fairly common.

Wilson and his co-workers,⁵ Bayley,⁶ and others have explained the nature of the cardiac vector and of the electric field which it produces. The reader is referred particularly to the section of Bayley's paper⁶ which deals with vectors and electricity. For present purposes, we need only start with the concept that, at the heart, there exists an electrical force, which has at any instant a magnitude and direction and which can, therefore, be represented by a vector. Surrounding this vector is a field with a potential distribution, every point of which possesses a definite potential. By the potential of a point we mean the work which would be done if we brought a hypothetical unit positive charge from an infinite distance to the point in question. By the potential difference between any two points, we mean the work which would be done if we moved this charge from one point to the other. If we say that the potential or the potential difference is positive, we mean that we have had to do work and expend energy in this transit. If we say that it is negative, we mean that the electric field has done the work for us. Now work is not a vector quantity because there is no direction associated with it. Thus, in Fig. 5, the work done in going from *A*, which has a potential of +5, to *B*, which has a potential of +10, is +5 units, regardless of how we get from *A* to *B*. There are certain parts of Part II where the field will do the work for us and other parts where we will have to do the work; but the excess of what we do over what the field does, is always five units. Hence, it should be evident that neither the potential at a point such as V_R , V_L , or V_F nor the potential differences such as e_1 , e_2 , and e_3 involve a special direction, and that they are not, therefore, vectors.

It may be well to take up at this time another point, which explains why $e_2 = e_1 + e_3$, a fact which has nothing whatever to do with Einthoven's triangle. Instead of taking two points in the field, let us take any three points and let us give them any potentials we choose. Further, let us call them *R*, *L*, and *F*, oriented quite at random (Fig. 5, *b*). Let us go from *R* to *L* to *F* and back to *R*, calling the work done between *R* and *L*, e_1 , between *L* and *F*, e_3 , and between *F* and *R*, e_2 (in order to retain the electrocardiographic notation). e_1 is then -8, which means that in going from *R* to *L* the field helps us by doing 8 units of work; e_3 is +112, which means that in going from *L* to *F* we have to do 112 units of work; e_2 is -104, which means that in going from *F* to *R* the field does 104 units of work. The net amount of work done is $-8 + 112 - 104$, which is zero. This is a general fact, and it tells us that whenever we go around a closed loop, of any shape, and return to the starting point, the net amount of work done is zero. This is true for any number of stopping points above two, the only condition being that we get back to the starting point.

In the example above, we have seen that $e_1 + e_2 + e_3 = 0$. Now, if we arbitrarily reverse the sign of the work done between any two points, then obviously this work will equal the sum of all the other work done. That is exactly what is done in electrocardiography. The attachments to the galvanometer are

such that we measure the work done (potential difference) in going from F to R instead of from R to F . Therefore, e_2 is arbitrarily given a negative sign and we obtain

$$e_1 - e_2 + e_3 = 0 \quad \text{or} \\ e_1 + e_3 = e_2.$$

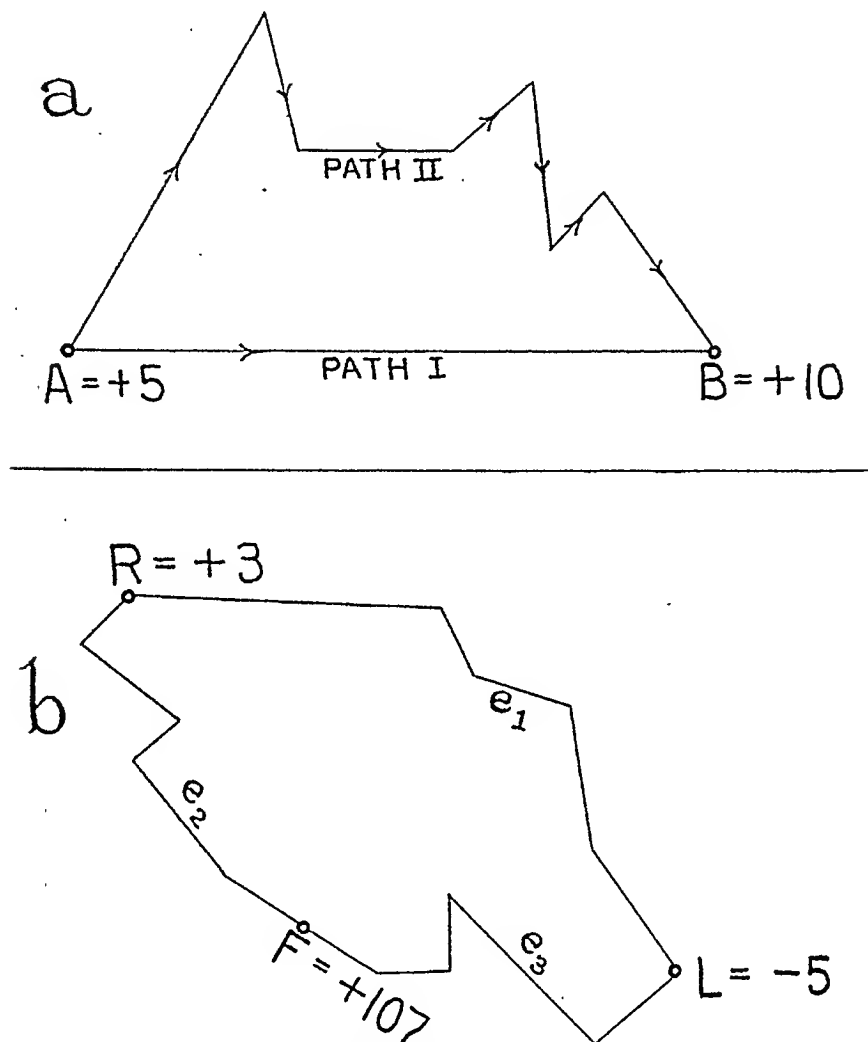


Fig. 5.—*a*, Two points in a scalar potential field. *b*, R , L , and F are any three points in a scalar potential field.

To return, then, to our original problem, in electrocardiography, R , L , and F are not oriented at random but are regarded as being located at the apices of an equilateral triangle. From what has been explained above, it is clear that none of the six quantities V_L , V_R , V_F , e_1 , e_2 , and e_3 has any necessary direction associated with it. These quantities are not vectors, but scalars, and, like all scalars, they can be added or subtracted in the same way that we can add two apples to eight apples or subtract two apples from eight apples. Therefore, it is possible to define e_1 as $V_L - V_R$, et cetera.

However, if we assign definite directions to these quantities, we can treat them as vectors. This is done, of course, by assigning to e_1 , e_2 , and e_3 the directions of the limb leads, i.e., the directions of the sides of the equilateral triangle; and by assigning to V_R , V_L , and V_F the directions OR , OL , and OF , respectively (Fig. 2). Now when these six quantities are transformed into vectors, they

must obey vector laws. They can no longer be simply added or subtracted. To illustrate what this means: if 1 is a scalar, then we can add 1 and 1 and obtain 2. If 1 is a vector, then the addition of two such vectors will give a resultant of 2 *only* when the two vectors are pointing in the same direction. If they make, for example, an angle of 90° with each other, then their sum is not 2 but $\sqrt{2}$. Hence it follows that, after becoming a vector, quantity e_1 is not necessarily equal to $V_L - V_F$. We have, in fact, given these six quantities six different directions.

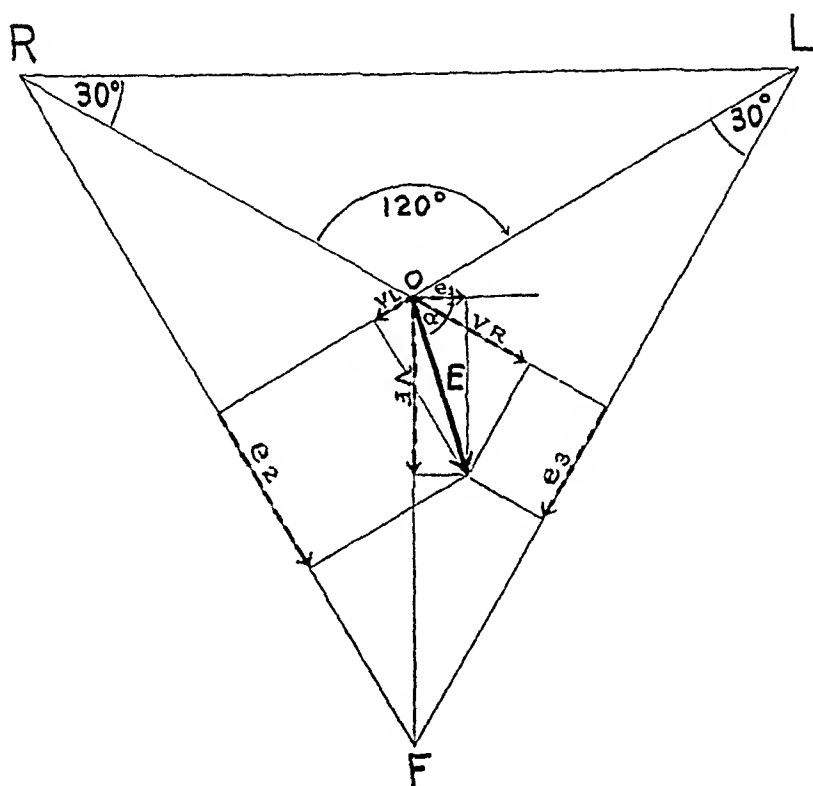


Fig. 6.—The six components of E are shown by broken lines, with arrowheads to denote that they are vectors. The magnitudes of the components can be expressed in terms of E and α . These magnitudes are given in the text.

The purpose in transforming these quantities into vectors is to enable us to treat these vectors as the projections or components of the cardiac vector E , which we call the "manifest potential difference" or the "electrical axis" of the heart. This is legitimate enough. Now, if e_1 is to be the projection of E in the direction of limb Lead I, then $V_L - V_F$, which has been defined as equal to e_1 , should also be the projection of E in the direction of Lead I. But the definition of e_1 as $V_L - V_F$ was based on the essentially scalar nature of these quantities and does *not* carry over when they become vectors. This means that if, as in Fig. 1, $V_L = +10$ and $V_R = -3$, e_1 does *not* equal $+13$. Similarly, e_2 and e_3 must be dealt with as vectors and not as scalars. If Fig. 3, constructed for *vector* values of V_L , V_R , and V_F is correct, then Fig. 1 must have been constructed from the wrong *vector* values of e_1 , e_2 , and e_3 and must therefore be incorrect with respect to Fig. 3. On the other hand, if the vector values $e_1 = +13$, $e_2 = -4$, and $e_3 = -17$ are correct, thereby making Fig. 1 correct, then Fig. 2 is incorrect because we have used the wrong values for V_R , V_L , and V_F .

To find our way out of this difficulty, we only need find out how the component of E in the direction of Lead I is related to the difference between the components in the directions of OL and OF . In other words, how is vector e_1 related to the vector $(V_L - V_F)$? Vectors e_2 and e_3 must be similarly studied. As a matter of fact, these relationships already have been worked out, although not in the exact form in which they apply to this problem.⁷ Fig. 6 should need no explanation. We must only keep in mind that all of the quantities used below are to be thought of as vectors. As usual, α is the angle between E and Lead I. Our six vectors are related to E and α by the following relationships:

$$\begin{aligned} e_1 &= E \cos \alpha \\ e_2 &= E \cos (\alpha - 60^\circ) \\ e_3 &= E \cos (120^\circ - \alpha) \\ V_R &= E \cos (210^\circ - \alpha) \\ V_L &= E \cos (\alpha + 30^\circ) \\ V_F &= E \sin \alpha \end{aligned}$$

The only other relationship we need is the familiar trigonometric one, $\cos (A \pm B) = \cos A \cos B \mp \sin A \sin B$.

Then

$$V_L - V_R = E \left[\cos (\alpha + 30^\circ) - \cos (210^\circ - \alpha) \right],$$

$$V_L - V_R = E \left[\frac{\sqrt{3}}{2} \cos \alpha - \frac{1}{2} \sin \alpha + \frac{1}{2} \sqrt{3} \cos \alpha + \frac{1}{2} \sin \alpha \right].$$

$$\therefore V_L - V_R = E \cos \alpha \cdot \sqrt{3} = e_1 \sqrt{3}.$$

Similarly

$$V_F - V_R = E \left[\sin \alpha - \cos (210^\circ - \alpha) \right], \text{ and}$$

$$V_F - V_R = E \left[\frac{3}{2} \sin \alpha + \frac{1}{2} \sqrt{3} \cos \alpha \right].$$

$$\text{But } e_2 = E \cos (\alpha - 60^\circ) = E \left[\frac{1}{2} \cos \alpha + \frac{1}{2} \sqrt{3} \sin \alpha \right].$$

Multiplying both sides by $\sqrt{3}$, we get

$$\sqrt{3} e_2 = E \left[\frac{\sqrt{3}}{2} \cos \alpha + \frac{3}{2} \sin \alpha \right].$$

$$\therefore V_F - V_R = e_2 \sqrt{3}.$$

Similarly

$$V_F - V_L = E \left[\sin \alpha - \cos (\alpha + 30^\circ) \right], \text{ and}$$

$$V_F - V_L = E \left[\frac{3}{2} \sin \alpha - \frac{1}{2} \sqrt{3} \cos \alpha \right].$$

$$\text{But } e_3 = E \cos (120^\circ - \alpha) = E \left[\frac{1}{2} \sqrt{3} \sin \alpha - \frac{1}{2} \cos \alpha \right].$$

Multiplying both sides by $\sqrt{3}$, we get

$$\sqrt{3} e_3 = E \left[\frac{3}{2} \sin \alpha - \frac{1}{2} \sqrt{3} \cos \alpha \right].$$

$$\therefore V_F - V_L = e_3 \sqrt{3}.$$

Summarizing,

$$V_L - V_R = e_1 \sqrt{3}$$

$$V_F - V_R = e_2 \sqrt{3}$$

$$V_F - V_L = e_3 \sqrt{3}$$

The reason for the discrepancy between Figs. 1 and 3 is now obvious. Both constructions are perfectly valid but differ from each other by the proportionality constant $\sqrt{3}$. Therefore, two procedures are open to us: (a) We can use Method I, unchanged, on the limb lead potentials. However, if we then wish to use Method II on V_L , V_R , and V_F , we must make an adjustment either by multiplying V_L , V_R , and V_F each by $\sqrt{3}$ before constructing E , or by constructing E first and then multiplying its value by $\sqrt{3}$. (b) We can use Method II unchanged on V_R , V_L , and V_F . However, if we then wish to use Method I on e_1 , e_2 , and e_3 , we must adjust either by dividing these values by $\sqrt{3}$ before constructing E , or by constructing E first and then dividing it by $\sqrt{3}$.

Since the equations defining these vector relationships contain no angles, either method, unaltered, will give the correct orientation of E .

As Wilson⁸ and others have pointed out, the construction of the cardiac vector, E , is a very useful tool in clinical analysis, even though the vector so obtained does not give the actual magnitude* but only a quantity proportional to it. We have discussed in this paper another proportionality factor which must be taken into account when different methods of construction are used. To put the matter in simple comparative terms, it is as though Method I gives the value of E in feet, and Method II in yards, whereas E might really be expressible in miles. If we imagine that the relationship between the mile on the one hand, and feet and yards on the other, is unknown or unmeasured, then we will get a good picture of the actual significance of these constructions.

SUMMARY

1. Two methods of constructing the cardiac vector, E , differ from each other by a factor $\sqrt{3}$.

2. The quantities measured in electrocardiography are essentially scalar in nature; from this fact the independence of the relationship $e_1 + e_3 = e_2$, of Einthoven's triangle, follows.

3. The significance of a transformation of V_L , V_R , V_F , e_1 , e_2 , and e_3 into vectors was discussed. The relationship between these vectors was obtained and it was shown that both methods of construction are valid and equivalent and can be equalized, if one makes certain adjustments to account for the difference in orientation of the two triaxial reference systems.

The author wishes to thank Dr. Emmanuel Goldberger for calling the problem to her attention and Dr. Richard Ashman for his encouragement.

*The actual magnitude, as used here, refers to the magnitude of the projection of the spatial vector on the frontal plane. It was not necessary, in the above analysis, to discuss the three-dimensional cardiac vector.

REFERENCES

1. Goldberger, E.: Personal communication.
2. Wilson, F. N., Johnston, F. D., Macleod, A. G., and Barker, P. S.: Electrocardiograms That Represent the Potential Variations of a Single Electrode, *AM. HEART J.* 9: 447, 1934.
3. Goldberger, E.: A Simple, Indifferent, Electrocardiographic Electrode of Zero Potential and a Technique of Obtaining Augmented Unipolar, Extremity Leads, *AM. HEART J.* 23: 483, 1942.
4. Bayley, R. H.: On Notation, *AM. HEART J.* 25: 33, 1943.
5. Wilson, F. N., Macleod, A. G., and Barker, P. S.: The Distribution of the Action Currents Produced by Heart Muscle and Other Excitable Tissues Immersed in Extensive Conducting Media, *J. Gen. Physiol.* 16: 423, 1933.
6. Bayley, R. H.: On Certain Applications of Modern Electrocardiographic Theory to the Interpretation of Electrocardiograms Which Indicate Myocardial Disease, *AM. HEART J.* 26: 769, 1943.
7. Wilson, F. N., Macleod, A. G., and Barker, P. S.: The Potential Variations Produced by the Heart Beat at the Apices of Einthoven's Triangle, *AM. HEART J.* 7: 207, 1931.
8. Wilson, F. N., in Stroud, W. D.: *Diagnosis and Treatment of Cardiovascular Disease*, Philadelphia, 1940, F. A. Davis Company, vol. 1, p. 570.

THE INCIDENCE OF PALPABLE DORSALIS PEDIS AND POSTERIOR TIBIAL PULSATIONS IN SOLDIERS

AN ANALYSIS OF OVER 1,000 INFANTRY SOLDIERS

CAPTAIN JACOB J. SILVERMAN, M.C.
ARMY OF THE UNITED STATES

PALPATION for pulsations of peripheral arteries is an important clinical procedure. In the study of peripheral vascular diseases the presence or absence of a pulsation often gives a great deal of information. Pulsation may be absent in spasm, or as a result of organic changes in the palpated vessel. It is not sufficiently understood, however, that the absence of pulsation may also indicate a normal anatomic deviation. The radial artery pulsations are easily palpable and in normal individuals are rarely absent.

It has been a widely accepted opinion³ that the dorsalis pedis and posterior tibial pulsations almost always can be palpated in normal individuals, or at least are very rarely absent. Buerger¹ studied 200 patients in whom the presence of peripheral vascular disease was carefully ruled out and found only in one instance an absence of the dorsalis pedis pulsation. This low incidence of absence of pulsations (0.5 per cent) compares favorably with the findings in a similar study of 381 patients by Erb.² In Erb's series an absence of both posterior tibial pulsations was noted in two patients, and an absent pulsation of the dorsalis pedis and posterior tibial of one foot was noted in two patients. An absent pulse was, therefore, observed in less than 1 per cent of those patients who presented no evidence of peripheral vascular disease.

This low incidence of absent pulsations in normal individuals has been challenged by other investigators. Morrison,⁵ in an analysis of 1,000 individuals without symptoms of circulatory affections of the extremities, found an incidence of 19 per cent with absent pulsations of the dorsalis pedis and posterior tibial arteries. It should be mentioned that in Morrison's study two-thirds of the patients were women and that the ages varied widely. Reich⁶ studied 500 healthy individuals and noted an absence of the dorsalis pedis pulsation in 4 per cent and an absence of the posterior tibial pulsation in 5 per cent of the patients. In an additional 8 per cent of the patients the dorsalis pedis pulsation was found in a position other than the usual one. In Schneyer's⁷ analysis of 500 controls there was an absence of pulsation in 17 per cent of the men and 29 per cent of the women.

To supply further information on this problem the dorsalis pedis and posterior tibial pulsations were studied in 1,014 soldiers at an Army Infantry Training Center. Each soldier had completed his basic infantry training; the

Presented at the annual meeting of the American Heart Association, San Francisco, Calif., June 29, 1945.

Received for publication Sept. 1, 1945.

examination was part of the processing for overseas duty. As far as could be ascertained no soldier presented circulatory complaints of the lower extremities. The average age was 20 years; over 90 per cent of the soldiers examined were under 22 years of age. All the examinations were performed by the same medical officer. The subjects were divided into four groups, A, B, C, and D. Each group was examined at a different session, on a different day, but at a similar hour. Groups A, B, and C were composed of white men, and Group D was composed of Negroes. To insure accuracy Groups B and C were checked by another examiner. The pulsations were graded as "palpable" or "not palpable." Where a pulsation was weak, faint, or found at a slight distance from the usual location, it was considered palpable.

FINDINGS

A summary of the four groups examined is given in Table I. Of the 1,014 soldiers examined, 898, or 88.6 per cent, had a palpable right dorsalis pedis, and 116, or 11.4 per cent, had an absent right dorsalis pedis pulsation. In the

TABLE I. COMPOSITE TABLE OF PULSATIONS

GROUP	DORSALIS PEDIS RIGHT		POSTERIOR TIBIAL RIGHT		DORSALIS PEDIS LEFT		POSTERIOR TIBIAL LEFT	
	PALPABLE	NOT PALPABLE	PALPABLE	NOT PALPABLE	PALPABLE	NOT PALPABLE	PALPABLE	NOT PALPABLE
A	330	47	370	7	326	51	373	4
(white)								
377	87.5%	12.5%	98.1%	1.9%	86.3%	13.7%	98.9%	1.1%
B	234	38	263	9	237	35	265	7
(white)								
272	86.0%	14.0%	96.7%	3.3%	87.2%	12.8%	97.4%	2.6%
C	230	29	255	4	213	46	252	7
(white)								
259	88.8%	11.2%	98.5%	1.5%	82.2%	17.8%	97.3%	2.7%
D	104	2	97	9	101	5	97	9
(Negro)								
106	98.1%	1.9%	92.5%	7.5%	95.3%	4.7%	91.5%	8.5%
(A, B, C, D)	898	116	985	29	877	137	987	27
1,014	88.6%	11.4%	97.1%	2.9%	86.4%	13.6%	97.3%	2.7%

TABLE II. TABLE OF ABSENT PULSATIONS IN MORE THAN ONE ARTERY

GROUP	DORSALIS PEDIS AND POSTERIOR TIBIAL NOT PALPABLE RIGHT FOOT	DORSALIS PEDIS AND POSTERIOR TIBIAL NOT PALPABLE LEFT FOOT	DORSALIS PEDIS NOT PALPABLE BOTH FEET	POSTERIOR TIBIAL NOT PALPABLE BOTH FEET
A	0	1	25	3
(white)				
377	0.0%	0.3%	6.6%	0.8%
B	2	1	28	3
(white)				
272	0.7%	0.4%	10.3%	1.1%
C	0	1	22	3
(white)				
259	0.0%	0.4%	8.5%	1.2%
D	0	0	1	8
(Negro)				
106	0.0%	0.0%	0.9%	7.5%
(A, B, C, D)	2	3	76	17
1,014	0.2%	0.3%	7.5%	1.7%

left foot. 877 (86.4 per cent) had a palpable dorsalis pedis pulsation, and in 137 (13.6 per cent) this pulsation was absent. The posterior tibial pulsation on the right side was palpable in 985 (97.1 per cent) and absent in 29 (2.9 per cent). On the left side, the posterior tibial pulsation was palpable in 987 (97.3 per cent) and absent in 27 (2.7 per cent).

The number of absent pulsations in more than one artery is shown in Table II. Of the 1,014 soldiers examined, only two soldiers had an absent dorsalis pedis and an absent posterior tibial pulsation of the right foot, and in only three soldiers were these same pulsations absent in the left foot. There were 76 soldiers with an absent dorsalis pedis pulsation in both feet, an incidence of 7.5 per cent. In 17 soldiers there was an absence of both the posterior tibial pulsations in both feet, an incidence of 1.7 per cent.

TABLE III. TABLE OF COMPARISON OF PULSATIONS IN WHITE AND NEGRO SOLDIERS

RACE	DORSALIS PEDIS RIGHT		POSTERIOR TIBIAL RIGHT		DORSALIS PEDIS LEFT		POSTERIOR TIBIAL LEFT	
	PALPABLE	NOT PALPABLE	PALPABLE	NOT PALPABLE	PALPABLE	NOT PALPABLE	PALPABLE	NOT PALPABLE
White (908)	794	114	888	20	776	132	890	18
	87.4%	12.6%	97.8%	2.2%	85.6%	14.5%	98.0%	2.0%
Negro (106)	104	2	97	9	101	5	97	9
	98.1%	1.9%	92.5%	7.5%	95.3%	4.7%	91.5%	8.5%

The frequency of pulsations in the white and in the Negro soldier is shown in Table III. A significant difference was found in the two races. Whereas the right dorsalis pedis pulsation was absent in 12.6 per cent of the white men, this pulsation was absent in only 1.9 per cent of the Negroes. On the left side of the dorsalis pedis pulsation was absent in 14.5 per cent of the white men and in only 4.7 per cent of the Negroes. The situation was reversed when the posterior tibial pulsations were examined: approximately 2 per cent of the posterior tibial pulsations were absent in the white group and 8 per cent in the Negro group. When the absence of pulsation in more than one artery was studied (Table IV), the white soldiers showed a higher percentage of absence of both dorsalis pedis pulsations, whereas the Negro soldiers showed a higher percentage of absence of bilateral posterior tibial pulsations. Absence of both a dorsalis pedis and a posterior tibial pulsation in the same foot was very unusual. This occurred only five times in the 1,014 soldiers examined. In only one soldier of the entire series was the absence of pulsation of both the dorsalis pedis and posterior tibial in both feet observed.

TABLE IV. TABLE OF COMPARISON OF ABSENT PULSATIONS IN MORE THAN ONE ARTERY OF WHITE AND NEGRO SOLDIERS

RACE	DORSALIS PEDIS AND POSTERIOR TIBIAL NOT PALPABLE RIGHT FOOT	DORSALIS PEDIS AND POSTERIOR TIBIAL NOT PALPABLE LEFT FOOT	DORSALIS PEDIS NOT PALPABLE BOTH FEET	POSTERIOR TIBIAL NOT PALPABLE BOTH FEET
White (908)	2	3	75	9
	0.2%	0.3%	8.3%	1.0%
Negro (106)	0	0	1	8
	0.0%	0.0%	0.9%	7.5%

DISCUSSION

A clinical study of the incidence of pulsations is subject to certain criticisms. The interpretation of a pulsation is subjective, and its accuracy depends to a large extent upon the efficiency and experience of the examiner. Moreover, the environment in which the examination is performed will influence the results. A cold room, for example, may cause a barely palpable vessel to become impalpable. Emotional factors may influence the results, and in anxiety states the caliber of the blood vessels may be profoundly reduced. The physical condition of the patient at the time of the examination may affect the results. Such other conditions as a deformity of the foot, varicosities, edema, or obesity may make it difficult to palpate a normal vessel. Most studies dealing with this problem include women, thus introducing further variables. It is important to emphasize that this study was performed on a group of healthy, young soldiers chosen for the infantry.

The arterial blood supply of the foot is derived mainly from two arteries, the anterior tibial and the posterior tibial. The dorsalis pedis artery is really a continuation of the anterior tibial artery, extending downward to the proximal portion of the first intermetatarsal space. The posterior tibial artery is a continuation of the popliteal artery and extends downward to the groove between the internal malleolus and os calcis. It is these two arteries with their extensive series of anastomoses which insure a proper arterial supply to the foot. In man, however, this architectural arrangement is subject to many variations. As Reich⁶ has pointed out, man differs from all other primates in this arterial distribution. In primates other than man, the blood supply of the foot comes directly from the femoral artery by way of a saphenous artery. This saphenous artery, not found in man, continues as the dorsalis pedis artery and gives off a posterior branch supplying the plantar aspect of the foot. This more direct arterial supply of the foot seen in other species of primates is therefore subject to less anatomic variation.

A normal variation of the arteries of the foot has been noted by anatomists. According to Gray⁴ the dorsalis pedis artery may be larger than usual to compensate for a deficient plantar vessel, and "in 12 per cent of the bodies examined the dorsal pedis artery was so small as to be considered absent." Although no figures were given, Gray⁴ noted that the posterior tibial artery was "not infrequently smaller than usual or absent." Clinically, therefore, one should normally expect to encounter absent dorsalis pedis and posterior tibial pulses in a small but definite percentage of cases. It was somewhat surprising, however, to find the incidence so high. Moreover, the incidence seemed to vary within the white and Negro races. This difference in frequency of pulses from a racial standpoint was commented upon by Reich,⁶ who found, for example, that 4.9 per cent of the Japanese on whom observations had been made had an absent posterior tibial artery, as compared with 8.7 per cent of Europeans. In this study it was found that an absence of the dorsalis pedis pulse was decidedly more common in white persons than in Negroes. The reverse was true of the posterior

tibial pulsation. It was unusual to find an absent posterior tibial in white soldiers (2 per cent), whereas in the Negro soldier an absent posterior tibial pulse was more common (8 per cent). Regardless of race, when the dorsalis pedis pulsation was absent, a good posterior tibial was invariably found; and similarly when the posterior tibial pulsation was absent, a good dorsalis pedis was found. In only five instances (0.49 per cent) of the entire series of 1,014 subjects was this finding violated. This is understandable when one considers the architectural arrangement of the arteries of the foot. The collateral circulation of the foot is dependent upon an adequate anastomosis of the posterior tibial and dorsalis pedis arteries. It is apparent, then, that a reduction in the size of the dorsalis pedis artery, for example, will be accompanied by a corresponding increase in the size of the posterior tibial artery. From a practical standpoint it is well to remember that in normal individuals an absence of both the dorsalis pedis and posterior tibial pulsations on the same side is anatomically unsound and decidedly uncommon. An absent dorsalis pedis and posterior tibial pulse on the same side would, therefore, seem to have more clinical significance than an absence of bilateral dorsalis pedis or an absence of bilateral posterior tibial pulsations. The order of importance to be attached to normal absence of pulsation in soldiers of the two races is shown in Table V.

TABLE V. PULSATIONS OF FOOT ARRANGED ACCORDING TO ORDER OF ABSENCE

WHITE	NEGRO
1. Left dorsalis pedis (14.5%)	1. Left posterior tibial (8.5%)
2. Right dorsalis pedis (12.6%)	2. Right posterior tibial (7.5%)
3. Right and left dorsalis pedis (8.3%)	3. Right and left posterior tibial (7.5%)
4. Right posterior tibial (2.2%)	4. Left dorsalis pedis (4.7%)
5. Left posterior tibial (2%)	5. Right dorsalis pedis (1.9%)
6. Right and left posterior tibial (1%)	6. Right and left dorsalis pedis (0.9%)
7. Left dorsalis pedis and left posterior tibial (0.3%)	7. Right dorsalis pedis and right posterior tibial (0%)
8. Right dorsalis pedis and right posterior tibial (0.2%)	8. Left dorsalis pedis and left posterior tibial (0%)

SUMMARY

1. The incidence of palpable dorsalis pedis and posterior tibial pulsations was studied in 1,014 infantry soldiers; in over 13 per cent one or more pulses was absent.

2. The incidence of palpable pulsations in these arteries was different in white and Negro soldiers. The posterior tibial pulse was more frequently absent in the Negro, and the dorsalis pedis pulse was more frequently absent in the white soldier.

3. Absence of both the dorsalis pedis and the posterior tibial pulses on the same side was most unusual. This combination occurred in only five instances of the entire series.

4. The posterior tibial and dorsalis pedis arteries in man are subject to wide anatomic variations. In interpreting an absent pulsation in the foot one should be aware of these normal variations.

REFERENCES

1. Buerger, L.: The Circulatory Disturbances of the Extremitis, Philadelphia, 1924, W. B. Saunders Co.
2. Erb, W.: Ueber das "intermittirende Hinken" und andere nervose Störungen in Folge von Gefässerkrankungen, Deutsche Ztschr. f. Nervenhe. 13: 1, 1898.
3. Formijne, P.: Investigation of the Patency of Peripheral Arteries, AM. HEART J. 10: 1, 1934.
4. Gray, H.: Anatomy of the Human Body, ed. 24, Philadelphia, 1942, Lea & Febiger.
5. Morrison, H.: A Study of the Dorsalis Pedis and Posterior Tibial Pulses in One Thousand Individuals Without Symptoms of Circulatory Affections of the Extremities, New England J. Med. 208: 438, 1933.
6. Reich, R. S.: The Pulses of the Foot; Their Value in the Diagnosis of Peripheral Circulatory Disease, Ann. Surg. 99: 613, 1934.
7. Schneyer: (Cited by Formijne³) Deutsche med. Wehnschr. 50: 109, 1924.

THE RATES OF WATER AND HEAT LOSS FROM THE RESPIRATORY
TRACT OF PATIENTS WITH CONGESTIVE HEART FAILURE
WHO WERE FROM A SUBTROPICAL CLIMATE AND
RESTING IN A COMFORTABLE ATMOSPHERE

G. E. BURCH, M.D.*
NEW ORLEANS, LA.

BECAUSE of the importance of the disturbances in water balance in congestive heart failure, any knowledge of the nature of water loss from the respiratory tract is significant. The dyspnea and accumulation of water in the lungs in congestive heart failure makes a study of this sort even more interesting. As shown previously,¹ the rate of heat and water loss is influenced by the conditions of the environment, particularly hot and humid environments. The latter type of environment was found to disturb the patient in congestive heart failure a great deal² thus further increasing the need of a study of water and heat loss from the respiratory tract in heart failure. Such observations are wanting, for a review of the literature revealed only one paper³ concerned with such studies. With these facts in mind, a study was undertaken to investigate quantitatively the rates of water and heat loss from the respiratory tract of patients with congestive heart failure who rested sitting in a comfortable atmosphere.

METHODS AND MATERIALS

The methods employed for the measurement of water and heat loss were described previously.⁴ Space does not permit a repetition of the description of the methods in detail in this report. In brief, the water loss was measured by having the subjects exhale through aluminum coils cooled by carbon dioxide snow. By means of suitable valves and gas meters the subjects would inspire room air and expire the water laden air through the collecting coils where the water was condensed. Simultaneously, the water content of an equal volume of room air was measured by the same method. The volume of air irrigating the respiratory tract per unit of time was recorded by the gas meters. By weighing the aluminum coils on an analytical balance before and after the collecting of the water and simultaneously measuring the water content of the air inspired, the rate of water loss from the respiratory tract became known.

To measure the heat loss simultaneously with the measurement of water loss from the respiratory tract, thermocouples were inserted in the afferent and efferent paths of the respired air. This made it possible to learn the heat exchange by warming or cooling inspired air. From the water loss, heat loss from evaporation was calculated. From the volume of carbon dioxide liberated, the heat loss from the decomposition of carbonic acid was learned. The total rate of

Added by the Rockefeller Foundation and the Hells Institute for Medical Research.
Received for publication Dec. 12, 1915.

*From the Department of Medicine, Tulane Medical School, and the Charity Hospital, New Orleans, La.

heat loss from the body was measured by the ordinary clinical type of basal metabolism apparatus. From these methods (see previous report⁴ for details) it was possible to measure quantitatively: (1) the rate of respiration, (2) the volume of tidal air, (3) the rate of irrigation of the respiratory tract with air, (4) the rate of carbon dioxide liberation, (5) the rate of heat loss from carbon dioxide liberation, (6) the rate of water loss, (7) the rate of heat loss from the evaporation of water, (8) the temperature of the expired air, (9) the relative humidity of the expired air, (10) the heat loss or gain by the warming or cooling of inspired air, (11) the relationships of each component of heat loss from the respiratory tract to the total heat loss, and (12) the relationship of heat loss from the respiratory tract to total body heat loss.

The 24 subjects employed in these studies suffered from uncomplicated right and left congestive heart failure. The etiology of the failure varied; hypertension, arteriosclerosis, syphilis, rheumatic fever, or "toxic" myocarditis (precise nature unknown) was the cause in descending order of frequency. The age, sex, and color distributions are indicated by Tables I and II. All of the patients were in Functional Class IV⁵ during the studies, except for Subjects 1 and 2, whose state of cardiac function varied while under repeated observations for several weeks. Although all of the patients were bedridden because of their heart failure, none of them were in a state of peripheral circulatory collapse and none were moribund. All of them had marked dyspnea, orthopnea, fine moist râles in the bases of the lungs, edema of the feet and legs, a large liver, and the other usual symptoms and signs of congestive heart failure. With only two exceptions the patients showed either beginning cardiac compensation or no change in the functional capacity of the heart. In the two subjects the state of the heart failure was progressively becoming worse during hospitalization and study. All patients were receiving treatment for congestive heart failure. This included bed rest, low salt intake, digitalis, and diuretics, including intravenous mercurial diuretics. Two subjects had auricular fibrillation.

The subjects were transported from Charity Hospital to the laboratory at Tulane. They rested in the sitting position during the entire study, resting for at least thirty minutes before any observations were begun. It required approximately thirty minutes to complete the observations. The conditions of the environment are indicated by Tables I and II. Repeated measurements were made on some of the subjects. All patients were dressed in a cotton hospital type of gown and then covered from the waist down with a cotton sheet.

During the course of the study of these patients, patients with other disease states and normal subjects were observed as controls. The results on the normal subjects were reported previously.¹ Data from the paper will be employed freely for purposes of comparison. The studies on the patients with other disease states will be reported in detail as a group at a later date.

RESULTS

The results are summarized by Tables I and II and Figs. 1 and 2.

The Rate of Water Loss.—In a comfortable environment with a mean temperature of 20.1° C. (extremes, 19.5° and 21.1°) and a mean relative humid-

ity of 56 per cent (extremes, 47 and 67),* the mean rate of water loss for the 24 patients with congestive heart failure was 0.944 Gm. per square meter of surface area per ten minutes, the extremes being 0.625 and 1.482 (Table I). When the room conditions were changed slightly by raising the temperature 1.4° C. (mean, 21.5° C.; extremes, 21.1° and 22.2°) and lowering the relative

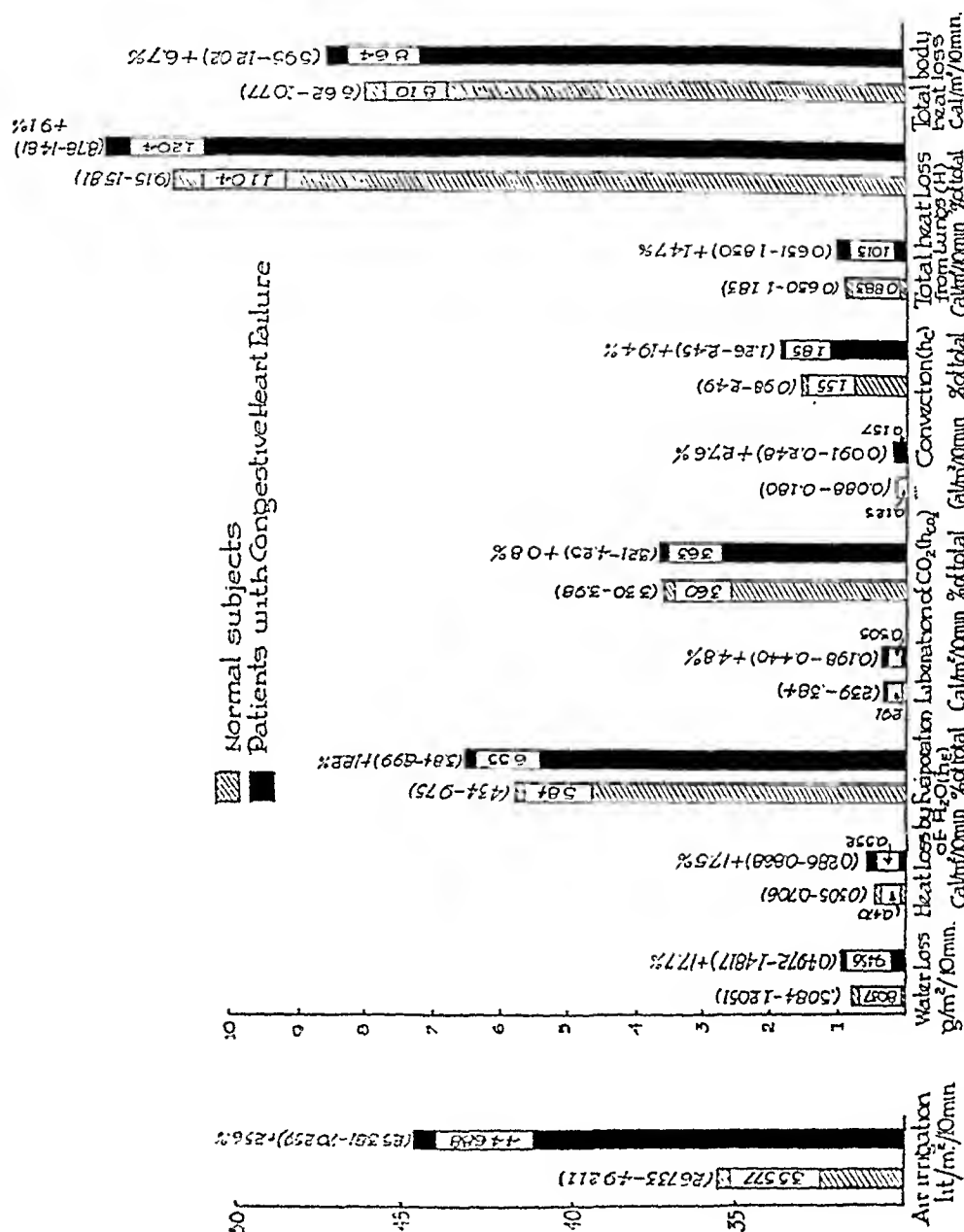


Fig. 1.—A graphic representation of the rates of irrigation of the respiratory tract with air and the rates of water and heat losses from the respiratory tract of normal subjects and patients with right and left ventricular congestive heart failure (functional Class IV). The mean values are indicated within the columns and the extreme values as shown in the parentheses above the columns. The percentage values represent the degree that the values are greater in congestive heart failure than in the normal.

humidity somewhat (mean, 51 per cent, extremes, 43 and 57),* the rate of water loss remained essentially unchanged (mean, 1.052; extremes, 0.694 and 1.456 Gm. per square meter of surface area per ten minutes). Under both environmental conditions the room atmosphere was comfortable. The statistical constants are shown in Tables I and II.

*This will be known as the comfortable environment at 20° C. and the comfortable environment at 21.5° C.

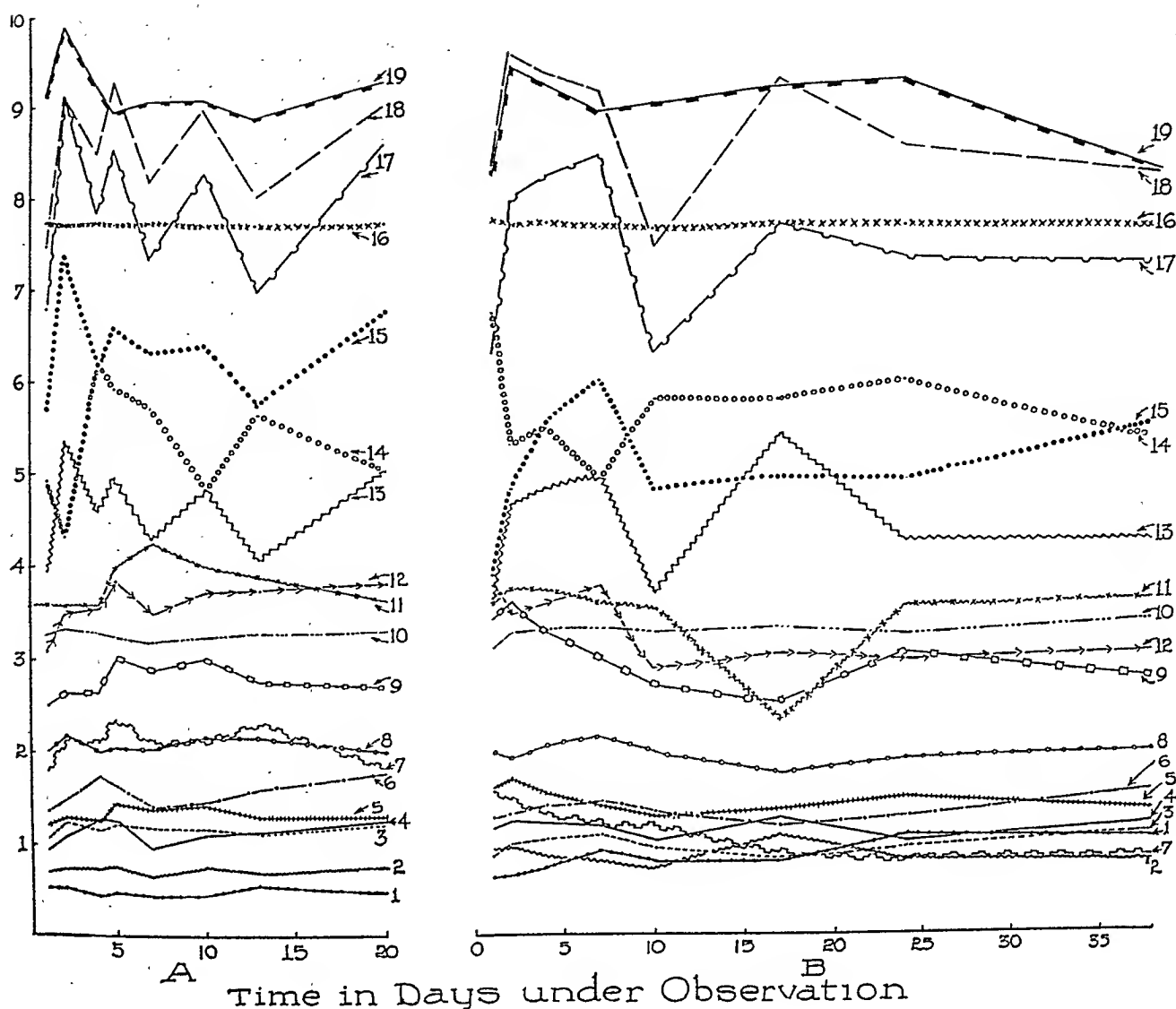


Fig. 2.—The results of repeated measurements upon two patients with congestive heart failure studied over a period of three or more weeks. A shows the results upon Patient 1 and B on Patient 2. The various lines shown represent the measurements and units indicated. In order to use a common ordinate the true value, V , was reduced or increased by multiples of ten as indicated. 1 = respiratory volume in c.c. $\frac{V}{(1000)}$. 2 = Rate of total body heat loss in calorie per square meter of surface area per ten minutes $\frac{(V)}{10}$. 3 = Rate of total loss of heat from the respiratory tract. H , in calorie/ M^2 surface area/ten minutes $(V \times 10)$. 4 = Rate of heat loss by convection, h_c , from the respiratory tract in calorie/ M^2 /ten minutes $(V \times 10)$. 5 = Rate of carbon dioxide loss in liters/ M^2 /ten minutes (V) . 6 = Rate of heat loss by convection, h_c , as percentage of total body heat loss $(V \times 10)$. 7 = Rate of respiration in minutes $\frac{(V)}{10}$. 8 = Dry bulb temperature of environment in $^{\circ}C$. $\frac{(V)}{10}$. 9 = Rate of heat loss from carbon dioxide excretion, h_{co_2} , in calorie/ M^2 /ten minutes $(V \times 10)$. 10 = Temperature of the expired air in $^{\circ}C$. $\frac{(V)}{10}$. 11 = Rate of heat loss from the excretion of carbon dioxide as percentage of total body heat loss in calorie/ M^2 /ten minutes (V) . 12 = Rate of irrigation of the respiratory tract with air in liters/ M^2 /ten minutes $\frac{(V)}{10}$. 13 = Rate of heat loss by the vaporization of water, h_v , in calorie/ M^2 /ten minutes $(V \times 10)$. 14 = Relative humidity of the room air in percentage $\frac{(V)}{10}$. 15 = Rate of heat loss by the vaporization of water as percentage of total body heat loss in calorie/ M^2 /ten minutes (V) . 16 = Barometric pressure of room atmosphere in mm. Hg $\frac{(V)}{100}$. 17 = Rate of water loss in grams/ M^2 /ten minutes $(V \times 10)$. 18 = Rate of total heat loss from the respiratory tract in calorie/ M^2 /ten minutes $(V \times 10)$. 19 = Relative humidity of the expired air in percentage $\frac{(V)}{10}$.

TABLE I. THE CONDITIONS OF THE ROOM ATMOSPHERE AND THE RATES OF WATER AND HEAT LOSSES FROM THE RESPIRATORY TRACT OF TWENTY-ONE PATIENTS WITH FUNCTIONAL CLASS IV RIGHT AND LEFT VENTRICULAR CONGESTIVE HEART FAILURE. THE PATIENTS RESTED SITTING QUIETLY IN A COMFORTABLE ROOM AT 20.1° C.

		RATE OF HEAT LOSS																					
SUBJECT	AGE	YR.	SEX	RACE		ENVIRON- MENT	D. B.†	R. H.‡	AIR IRRI- GATING LUNGS	CO ₂ EX- HALED	EXP. AIR	D. B.†	R. H.‡	WATER LOSS	VAPORIZED WATER		LIBERATION OF CO ₂		WARMING AIR		TOTAL LOSS FROM LUNGS		TOTAL BODY HEAT LOSS
															GM./M. ² / 10*	CAL./M. ² / 10*	% TOTAL	CAL./M. ² / 10*	% TOTAL	CAL./M. ² / 10*	% TOTAL	CAL./M. ² / 10*	
1	41	F	N		20.1	49	34.202	31.2	91	0.6766	0.396	5.66	0.252	3.60	0.096	1.37	0.744	10.65	7.00				
					19.9	62	35.601	33.1	92	0.7755	0.454	6.17	0.264	3.59	0.127	1.73	0.845	11.48	7.36				
					20.6	59	38.350	32.7	89	0.8492	0.498	6.55	0.303	3.99	0.125	1.64	0.926	12.18	7.60				
					20.3	57	35.189	32.0	90	0.7307	0.428	6.29	0.289	4.25	0.095	1.40	0.812	11.94	6.80				
					20.0	50	38.171	33.1	92	0.8543	0.501	6.74	0.270	3.63	0.125	1.68	0.896	12.06	7.43				
2	33	F	N		20.0	67	38.002	31.1	82	0.6252	0.366	3.91	0.339	3.63	0.118	1.26	0.823	8.80	9.35				
					19.5	53	34.667	32.8	94	0.7925	0.464	4.80	0.363	3.76	0.125	1.29	0.952	9.86	9.66				
					20.9	55	36.123	33.4	92	0.8220	0.482	5.53	0.327	3.75	0.122	1.40	0.931	10.68	8.72				
					20.0	53	28.713	33.1	90	0.6273	0.368	4.82	0.272	3.56	0.102	1.34	0.742	9.72	7.63				
					19.5	60	30.307	33.1	93	0.7336	0.430	4.93	0.312	3.58	0.113	1.30	0.855	9.81	8.72				
3	41	F	N		20.0	54	30.962	34.2	84	0.7344	0.430	5.52	0.285	3.66	0.120	1.54	0.835	10.72	7.79				
					20.0	47	63.796	31.7	94	1.4157	0.830	8.99	0.332	3.60	0.205	2.22	1.367	14.81	9.23				
					19.5	47	53.479	32.2	87	1.0912	0.639	7.86	0.289	3.55	0.186	2.29	1.114	13.70	8.13				
					20.6	67	49.412	32.5	84	0.9073	0.532	6.96	0.254	3.32	0.161	2.11	0.947	12.40	7.64				
					20.9	53	51.436	33.1	90	1.0640	0.624	7.54	0.302	3.65	0.172	2.08	1.098	13.26	8.28				
4	54	F	W		20.0	62	56.001	33.5	90	1.1830	0.693	8.20	0.307	3.63	0.207	2.45	1.207	14.28	8.45				
					20.6	59	41.187	32.2	87	0.8484	0.497	8.35	0.198	3.33	0.131	2.20	0.826	13.88	5.95				
					20.0	60	44.172	32.9	92	1.1582	0.679	6.93	0.346	3.53	0.169	1.72	1.194	12.18	9.80				
					20.0	50	50.212	32.8	89	1.0672	0.625	6.65	0.355	3.78	0.176	1.87	1.156	12.30	9.40				
					20.0	59	32.946	33.6	83	0.7410	0.434	5.75	0.274	3.63	0.122	1.62	1.830	10.99	7.55				
10	27	F	N		20.3	51	58.000	32.2	83	1.1430	0.667	7.60	0.310	3.53	0.189	2.15	1.116	13.28	8.78				
					20.3	57	63.055	33.4	83	1.1276	0.661	5.50	0.440	3.66	0.226	1.88	1.327	11.04	12.02				
					20.0	55	70.259	32.9	87	1.4817	0.868	8.27	0.387	3.69	0.248	2.36	1.503	14.31	10.50				
11	54	M	N																				
12	54	M	N																				

*All units are in M² per ten minutes.

†D. B. = Dry bulb.

‡R. H. = Relative humidity.

13	67	M	N	20.0	54	55.908	1.464	33.1	82	1.2063	0.707	8.29	0.307	3.60	0.200	2.34	1.214	14.23	8.53
14	52	M	N	20.3	56	44.204	1.442	33.6	91	1.0940	0.641	7.60	0.303	3.59	0.161	1.91	1.105	13.11	8.43
15	27	F	N	20.0	67	48.909	1.437	34.1	96	1.2034	0.692	8.41	0.302	3.67	0.188	2.28	1.182	14.36	8.23
16	44	F	W	20.3	63	44.232	1.446	33.7	79	0.8000	0.460	5.41	0.304	3.58	0.182	1.91	0.926	10.89	8.50
17	53	F	N	19.7	57	47.897	1.446	33.6	86	0.8773	0.504	6.09	0.304	3.67	0.182	2.20	0.990	11.96	8.28
18	49	M	W	20.5	57	25.381	1.075	33.6	83	0.5421	0.312	4.76	0.228	3.48	0.091	1.39	0.631	9.62	6.56
19	35	M	N	20.3	57	26.350	1.294	33.6	77	0.4972	0.286	3.84	0.272	3.65	0.096	1.29	0.654	8.78	7.45
Statistical constants				19.7	59	53.972	1.579	33.9	74	0.9638	0.554	5.89	0.332	3.53	0.201	2.23	1.096	11.66	9.40
				20.0	57	35.619	1.256	33.6	81	0.6801	0.391	5.37	0.264	3.63	0.132	1.81	0.787	10.81	7.28
						44.9285±	1.4471±	33.09±	87.6±	0.94429±	0.5525±	6.536±	0.3006±	3.632±	0.1597±	1.861±	1.0500±	12.050±	8.422±
Mean						1.8263	0.5627	2.09	1.5	0.05809	0.0334	0.174	0.0116	0.031	0.0084	0.078	0.0496	0.397	0.309
Range				19.5	47	25.381	0.944	31.1	74	0.4972	0.286	3.84	0.198	3.32	0.091	1.26	0.631	8.78	5.95
				21.1	67	70.259	2.096	34.2	96	1.4817	0.868	8.99	0.440	4.25	0.248	2.45	1.830	14.81	12.02
Standard deviation						16.020±	0.4936±	1.8±	13±	0.5096±	0.293±	1.53±	0.102±	0.27±	0.074±	0.08±	0.435±	3.48±	2.71±
						1.291	0.040	1.5	1	0.0411	0.024	0.12	0.008	0.02	0.006	0.06	0.035	0.28	0.22
Coefficient of variation						35.6±	3.41±	5.5±	14.8±	53.9±	53.0±	23.4±	33.93±	7.46±	46.34±	36.54±	41.4±	28.88±	32.18±
						3.2%	0.28%	0.6%	0.1%	5.5%	0.4%	1.9%	3.03%	0.61%	4.47%	3.320%	3.8%	2.52%	2.9%

TABLE 11. THE CONDITIONS OF THE ROOM ATMOSPHERE AND THE RATES OF WATER AND HEAT LOSSES FROM THE RESPIRATORY TRACT OF PATIENTS WITH FUNCTIONAL CLASS IV RIGHT AND LEFT VENTRICULAR CONGESTIVE HEART FAILURE. THE PATIENTS RESTED SITTING QUIETLY IN A COMFORTABLE ROOM AT 21.5° C.

SUBJECT	AGE YRS.	SEX	RACE	ENVIRON- MENT		AIR IRRIGAT- ING LUNGS	CO ₂ EX- HALED	EXPIRED AIR		WATER LOSS GM./M. ² /10*	VAPORIZED WATER		LIBERATION OF CO ₂		WARMING AIR		TOTAL LOSS FROM LUNGS		TOTAL BODY HEAT LOSS CAL./ M. ² / 10*
				D. B.†	R. H.‡		I _a /M. ² / 10*	D. B.†	R. H.‡		CAL./ M. ² / 10*	% TOTAL	CAL./ M. ² / 10*	% TOTAL	CAL./ M. ² / 10*	% TOTAL	CAL./ M. ² / 10*	% TOTAL	
1	44	F	N	21.8	43	34.886	1.259	33.3	99	0.9107	0.534	7.26	0.264	3.59	0.108	1.47	0.906	12.22	7.36
	44	F	N	21.7	48	37.266	1.444	32.5	90	0.8219	0.482	6.34	0.303	3.99	0.110	1.45	0.895	11.78	7.60
				21.7	56	37.388	1.310	32.8	88	0.6938	0.407	5.72	0.275	3.86	0.114	1.60	0.796	11.18	7.12
2	38	F	N	21.7	49	37.975	1.422	33.4	89	0.8438	0.494	5.99	0.299	3.62	0.120	1.45	0.913	11.07	8.25
22	35	M	N	21.1	56	57.469	1.488	33.6	83	1.0737	0.629	7.31	0.312	3.63	0.196	2.28	1.137	13.22	8.60
				21.1	41	57.178	1.769	33.4	89	1.3322	0.781	7.63	0.371	3.63	0.192	1.88	1.344	13.14	10.23
				21.1	56	58.365	1.769	32.8	90	1.2978	0.760	7.43	0.371	3.63	0.186	1.82	1.317	12.87	10.23
23	61	M	W	21.1	56	51.304	1.320	32.5	93	1.1506	0.674	8.73	0.277	3.59	0.160	2.07	1.111	14.39	7.72
24	31	M	N	21.4	51	42.070	1.515	33.4	85	0.8569	0.502	5.55	0.318	3.51	0.137	1.51	0.959	10.60	9.05
4	51	F	N	22.0	52	47.146	1.662	34.8	83	1.0740	0.629	6.74	0.349	3.74	0.165	1.77	1.143	12.25	9.33
10	59	M	N	21.1	44	50.175	1.451	33.4	85	1.1139	0.652	7.70	0.305	3.60	0.169	2.00	1.126	13.29	8.49
11	52	F	N	22.2	57	74.238	1.996	33.6	83	1.4560	0.853	7.39	0.419	3.63	0.231	2.00	1.503	13.02	11.54
				21.1	56	42.317	1.383	34.2	87	1.0548	0.618	7.67	0.290	3.60	0.152	1.89	1.060	13.15	8.06
Mean				21.5	51	48.286	1.522	33.4	88	1.0528	0.617	7.04	0.319	3.66	0.157	1.78	1.093	12.48	8.74
Range				21.1	43	37.266	1.259	32.5	83	0.6938	0.407	5.55	0.264	3.51	0.108	1.45	0.796	10.60	7.12
				22.2	57	74.238	1.996	34.8	99	1.4560	0.853	8.73	0.419	3.99	0.231	2.28	1.503	14.39	11.54
Standard deviation				11.417±		0.203±	0.203±	0.65±	4.6±	0.217±	0.126±	0.921±	0.044±	0.13±	0.031±	0.26±	0.208±	1.041±	1.15±
				2.245		0.040	0.043	0.13	0.9	0.043	0.025	0.181	0.009	0.03	0.006	0.05	0.011	0.204	0.23
Coefficient of variation				23.70±		13.34±	2.62%	1.94±	5.19±	20.62±	20.42±	13.08±	13.79±	3.52±	1.94±	14.38±	19.03±	8.34±	13.16±
				4.65%		2.62%		0.38%	1.02%	4.04%	4.00%	2.57%	2.70%	0.69%	0.38%	2.82%	3.73%	1.61%	2.58%

*AD units are in M.² per ten minutes.

†D. B. = Dry bulb.

‡R. H. = Relative humidity.

Temperature of the Expired Air.—The mean temperature of the expired air was 33.1°C . (extremes, 31.1 and 34.2) for the comfortable environment at 20°C . When the environment was changed to 21.5°C ., the mean temperature of the expired air was 33.4°C . (extremes, 32.5 and 34.8). The statistical constants are shown in Tables I and II.

Relative Humidity of the Expired Air.—The mean relative humidity of the expired air was 87 per cent (extremes, 82 and 94) when the patients were in the room at 20°C . When the temperature of the room was changed to 21.5°C . the mean value increased to 88 per cent (extremes, 83 and 96). The value of 96 per cent (Table I) is most probably an erroneous value. This was the only such value obtained under the above room conditions. The statistical constants are found in Tables I and II.

Rate of Irrigation of the Respiratory Tract With Air.—In the comfortable environment at 20°C ., the mean rate at which the respiratory tract was irrigated with air was 44.929 liters per square meter of body surface area per ten minutes (extremes, 25.381 and 70.259). In the room atmosphere at 21.5°C . the mean rate was 48.286 liters per square meter of body surface area per ten minutes (extremes, 37.266 and 74.238). The statistical constants are indicated by Tables I and II.

There was a high positive correlation between the rate of water loss and the rate of irrigation of the respiratory tract with air, the coefficient of correlation being 0.9346 ± 0.0144 . The coefficient of correlation between the rate of irrigation of the respiratory tract to the rate of total body heat production (oxygen consumption) was 0.6449 ± 0.0666 .

Rate of Heat Loss From the Respiratory Tract.—The mean rate of heat loss by the vaporization of water, h_e , 0.553 calorie per square meter of body area per ten minutes (extremes, 0.286 and 0.868) when the comfortable environment was at 20°C . and 0.617 (extremes, 0.407 and 0.853) when the environment was at 21.5°C . This represented an average of 6.55 per cent (extremes, 3.84 and 8.99) of the total heat lost from the body and about 54.5 per cent (extremes, 28.2 and 85.7) of the total heat lost from the respiratory tract.

The mean rate of heat loss by convection or warming inspired air, h_c , was 0.157 calorie per square meter of body area per ten minutes (extremes, 0.108 and 0.231) at the 21.5°C . environment. This represented a mean of about 1.85 per cent (extremes, 1.26 and 2.45) of the total heat lost from the body and about 15.5 per cent (extremes, 9 and 24.5) of the total lost from the respiratory tract.

The mean rate of heat loss by the decomposition of carbonic acid with the expiration of carbon dioxide, h_{CO_2} was 0.305 calorie per square meter of surface area per ten minutes (extremes, 0.198 and 0.440) for the comfortable temperature at 20°C . The mean rate was 0.319 calorie per square meter of body surface per ten minutes (extremes, 0.264 and 0.419) for the room temperature of 21°C . The heat lost from the expiration of carbon dioxide represented about 3.63 per cent (extremes, 3.32 and 4.25) of the total loss of body heat or 30.1 per cent (extremes, 19.6 and 43.4) of the total heat lost from the respiratory tract.

The mean rate of total loss of heat from the respiratory tract was 1.013 calories per square meter of body area per ten minutes (extremes, 0.631 and 1.830) when the comfortable room temperature was 20° C. and a mean of 1.093 (range, 0.796 to 14.81) of the total heat lost from the body.

The mean rate of total heat loss from the body was 8.20 calories per square meter of body surface area per ten minutes (extremes, 6.56 and 10.50) when the subjects rested in a comfortable environment at 20° C.; the mean rate was 8.74 (extremes, 7.12 and 11.54) at a room temperature of 21° C.

Individual variations for each component of heat loss are given in detail in Tables I and II.

Prolonged Period of Study in Two Patients.—Two patients with moderately severe right and left ventricular congestive heart failure (Functional Class IV) were studied repeatedly over a period of three to six weeks. One patient (Patient 1) had myocarditis of undetermined etiology and the other (Patient 2) had syphilitic aortic regurgitation. The first subject died two weeks after completion of the last observation (no autopsy obtained), and the other is still living but has remained in Functional Class III. During the entire period of study Patient 1 remained in Functional Class IV, showing only slight variations in the degree of failure. Patient 2 returned to Functional Class III and was in that state for the two final recordings noted in Fig. 2. Both patients were in their most severe state of failure during the initial observations. Patient 2 had a definite exacerbation of her failure during the tenth day of observation.

Fig. 2 summarizes in detail the fluctuations in the various physiologic phenomena recorded. It can be seen that, in the main, there are definite variations in the rates of water and heat losses. It was not until Patient 2 reached a fairly steady state of cardiac function (in Class III) that the observed phenomena became stabilized.

DISCUSSION

It can be seen from the results and especially from Fig. 1 that the rates of water and heat loss from the respiratory tract in congestive heart failure are greater than normal. These increases over the normal are essentially proportional and appear to conform to that which would be expected upon the basis of increased rates of irrigation of the respiratory tract with air (dyspnea) and metabolism. This fact is borne out by the percentage increases in value of the various physiologic phenomena observed. Consult Fig. 1 for the percentage change from the normal in patients with congestive heart failure. A study of Fig. 1 reveals that the increases in water and heat lost from the respiratory tract are more the result of the dyspnea with the resultant increase in the rate of irrigation of the respiratory tract with air than to an increase in the rate of metabolism associated with the congestive heart failure. For example, there was an increase of 25.6 per cent in the rate of irrigation of the respiratory tract with air, 17.7 per cent in the rate of water loss, 19.4 per cent in the rate of heat loss by warming inspired air, and 9.1 per cent in the total amount of heat loss from the respiratory tract. At the same time there was an increase of only 4.8 per cent in heat loss by the excretion of carbon dioxide and 6.7 per cent increase

in the metabolic rate. The rates of water loss and heat loss by convection which depend upon the rate of irrigation of the lungs with air showed the greatest degree of increase over the normal, while heat loss from carbon dioxide excretion, dependent mainly upon the rate of metabolism, showed relatively little increase over the normal. Therefore, the ventilation of the lungs and not metabolism was largely responsible for the differences noted between congestive heart failure and the normal.

As in the normal subjects,¹ there was a high positive correlation between the rate of irrigation of the respiratory tract with air and the rate of water loss, the coefficients of correlation being 0.914 ± 0.014 in the patients with congestive heart failure. These findings are to be expected since the amount of water vapor that might be conveyed away by air is dependent in a large measure upon the amount of air available.

Since the carrying capacity of a unit volume of inspired air was the same in both groups of studies, the possible causes for differences in the rates of water loss between the normal subjects and the patients with heart failure might be due to: (1) the presence of large amounts of free fluid in the alveoli and small bronchioles in the patients with left ventricular failure and pulmonary edema and (2) the dyspnea. All of the patients with heart failure had fine moist râles at the bases of the lungs and all had a moderate amount of dyspnea. None had gurgling râles or were frothing at the mouth and none suffered with severe dyspnea, shock, and marked apprehension. Since the mean relative humidity of the expired air was 88 per cent (extremes, 78 and 96.5) for the normal and 87 (extremes, 74 and 96) for the patients with heart failure, the same amount of water vapor was added to each unit volume of inspired air in spite of the dyspnea and the extra amount of free fluid in the lungs in the patients with heart failure. The surface area of the pulmonary epithelium was probably reduced by the accumulation of fluid in the heart failure patients; but either because of insufficient change in the area or because of an increase of the vapor tension above the edema fluid, the relative humidity of the expired air did not change significantly from normal. The total amount of water lost in left ventricular congestive heart failure via the respiratory tract was 25.6 per cent greater than that for the normal under comparable conditions because of the dyspnea and the resultant rapid rate of irrigation of the respiratory tract with air. Obviously, the rate of heat loss by the vaporization of water follows the same principles and arguments governing water loss just described.

Under similar atmospheric conditions the temperature of the air expired by the normal subjects was 33.2°C . (extremes, 31.6 and 34.2) while the temperature of the air expired by patients with congestive heart failure was 33.0°C . (extremes, 31.1 and 34.2). As in the case of the relative humidity of the expired air, the presence of fluid in the lungs and the dyspnea did not interfere significantly with the warming of inspired air. The rate of heat loss by convection was 27.6 per cent greater in the patients with congestive heart failure, however. This increase was due to the greater rate of irrigation of the respiratory tract with air.

Since the rate of metabolism was only 6.7 per cent greater in the patients with congestive heart failure, and since the excretion of carbon dioxide is mainly dependent upon the rate of metabolism, the heat loss from the decomposition of carbonic acid in the lungs resulted only in a relatively slight increase in the rate of heat loss by carbon dioxide excretion. Therefore, the greater rate of heat loss (9.1 per cent) in congestive heart failure was due to an increase in the rate of heat loss by vaporization and convection.

The total body heat loss was not determined directly but was estimated by, first, measuring the rate of heat production from the rate of oxygen consumption and, second, assuming that the subject resting for sixty minutes in the comfortable room was in a state of thermal equilibrium with the environment. It is obvious that such an estimation of total body heat loss is subject to error. This may explain the finding that there was an increase above the normal of 9.1 per cent in heat loss from the lungs with only a 6.7 per cent increase in total body heat loss, a difference of 2.4 per cent. It is more likely, however, that this difference is due in large part to the dyspnea with the associated rapid rate of ventilation of the respiratory tract with air and the resultant increase in heat loss by vaporization of water and convection of heat. Obviously, such a discrepancy could exist for only a short period of time, as during a paroxysm of dyspnea, or there would result an associated decrease in body heat. The nature of the above studies rendered it impossible to evaluate such phenomena.

SUMMARY

A study of the rates of water and heat loss from the respiratory tract of 24 resting sitting patients with right and left ventricular congestive heart failure (Functional Class IV) and living in the subtropical climate of New Orleans showed the following when the room atmosphere was comfortable (temperature, 20.1° C.; relative humidity, 56 per cent):

1. The mean rate of water loss from the respiratory tract was 0.944 Gm. per square meter of body area per ten minutes (extremes, 0.625 and 1.482). When the room temperature was increased from 20.1° C. to 21.5° C., the mean rate of loss was essentially unchanged (mean, 1.052; extremes, 0.694 and 1.456).

2. The mean temperature of the expired air was 33.1° C. (extremes, 31.1 and 34.2). The values were 33.4° C. (extremes, 32.5 and 34.8) when the room temperature was increased to 21.5° C.

3. The mean relative humidity of the expired air was 87 per cent (extremes, 82 and 94). The value became 88 per cent (extremes, 83 and 96) when the room temperature was changed to 21.5° C.

4. The mean rate of irrigation of the respiratory tract with air was 44.929 liters per square meter of body area per ten minutes (extremes, 25.381 and 70.259). When the room temperature was increased to 21.5° C. these values became 48.286 liters (extremes, 37.266 and 74.238).

5. There was a high correlation between the rates of water loss and irrigation of the respiratory tract with air, the coefficient of correlation being 0.934 ± 0.0144.

6. The mean rate of heat loss from the respiratory tract by the vaporization of water, h_e , was 0.553 calorie per square meter of body area per ten minutes (extremes, 0.286 and 0.868). The values became 0.617 (extremes, 0.407 and 0.853) when the room temperature was raised to 21.5° C. This represented 6.55 per cent (extremes, 3.84 and 8.99) of the total heat lost from the body and 54.5 per cent (extremes, 28.2 and 85.7) of the total heat lost from the respiratory tract.

7. The mean rate of heat loss by convection, h_c , or warming inspired air was 0.157 calorie per square meter of body area per ten minutes (extremes, 0.091 and 0.248). The values became 0.157 (extremes, 0.108 and 0.231) when the room temperature was changed to 21.5° C. This represented a mean of 1.85 per cent (extremes, 1.26 and 2.45) of the total heat lost from the body and 15.5 per cent (extremes, 9 and 24.5) of the total lost from the respiratory tract.

8. The mean rate of heat loss by the decomposition of carbonic acid and excretion of carbon dioxide, h_{CO_2} , was 0.305 calorie per square meter of body area per ten minutes (extremes, 0.198 and 0.440). The value became 0.319 (extremes, 0.264 and 0.419) when the room temperature was increased to 21.5° C. This represented 3.63 per cent (extremes, 3.32 and 4.25) of the total heat lost from the body and 30.1 per cent (extremes, 19.6 and 43.4) of the total heat lost from the respiratory tract.

9. The mean total rate of heat loss from the respiratory tract was 1.013 calorie per square meter of body area per ten minutes (extremes 0.631 and 1.830). The values became 1.093 (extremes, 0.796 and 1.503) when the room temperature was increased to 21.5° C. This represented 12.04 per cent (extremes, 8.78 and 14.81) of the total heat lost from the body.

10. The rates of water and heat loss from the respiratory tract of patients with left and right ventricular congestive heart failure (Function Class IV) were definitely greater than the rates observed under similar conditions in 107 normal subjects. These increases were due in a large measure to the dyspnea and associated increased rate of irrigation of the respiratory tract with air. The extra amount of edema fluid in the lungs apparently influenced the results very little. A theoretical discussion of the principles concerned is presented.

An appreciation for the keen interest and significant technical assistance of Mr. G. Morgavi is expressed.

REFERENCES

1. Burch, G. E.: The Rate of Water and Heat Loss From the Respiratory Tract of Normal Subjects in a Subtropical Climate, *Arch. Int. Med.* 76: 315-327, 1945.
2. Burch, G. E.: The Rate of Water Loss From the Skin of Patients in Congestive Heart Failure in a Subtropical Climate, *Am. J. M. Sc.* 211: 181-188, 1946.
3. Calabresi, M., and Rocchini, G.: Water Metabolism in the Lungs in Decompensated Heart Disease, *Clin. med. ital.* 68: 519-533, 1937.
4. Burch, G. E.: A Study of Water and Heat Loss From the Respiratory Tract of Man. Methods: I. A Gravimetric Method for the Measurement of the Rate of Water Loss. II. A Quantitative Method for the Measurement of the Rate of Heat Loss, *Arch. Int. Med.* 76: 308-314, 1945.
5. Nomenclature and Criteria for Diagnosis of Diseases of the Heart by the New York Heart Association, New York, 1942.

WOLFF-PARKINSON-WHITE SYNDROME

A CLINICAL STUDY WITH REPORT OF NINE CASES

CAPTAIN DAVID LITTMANN, M.C., AND MAJOR HERMAN TARNOWER, M.C.
ARMY OF THE UNITED STATES

THE number of cases reported during the past few years would indicate that the syndrome of a "short PR interval with a prolonged, aberrant QRS complex" occurs much more frequently than has hitherto been realized. The criteria for diagnosis have been modified and the theories which have been advanced in explanation of the findings have become more numerous and involved.

Though the anomaly had been reported previously,^{9, 18} Wolff, Parkinson, and White²¹ were the first to present a group of cases that illustrated all of the common features. Their original article suggested that increased vagus tone was responsible for the short P-R interval and QRS prolongation. This appeared to be confirmed in those instances in which exercise or the administration of atropine produced a normal electrocardiographic pattern. As has been pointed out,¹⁵ this theory implies a paradoxical effect of vagus tone with a simultaneous exercise of two diametrically opposed influences, one accelerating conduction between auricles and ventricles with shortening of the P-R interval, the other retarding conduction through the bundle of His giving rise to the lengthening and distortion of the QRS complex.

Hunter, Papp, and Parkinson¹¹ later suggested that the electrocardiographic findings could be explained as being the result of a "fusion beat," on the basis of a "double rhythm" in which the auricular impulse fuses with a beat which arises in one bundle branch. They postulated two centers bearing a constant relationship. The hypothesis explains many of the findings but it is difficult to accept when other simpler mechanisms based on anatomic findings and experimental demonstrations are available. Also, as has been demonstrated, premature auricular beats may be followed by the usual distorted QRS complex.²⁰

The most satisfactory explanation to date was initially advanced by Holzmänn and Scherf in 1932¹⁰ and by Wolferth and Wood in 1933,¹⁹ and is based on the hypothesis of an accessory pathway of A-V conduction with ventricular asynchronism as a result of the premature stimulation of one ventricle.

The existence of accessory neuromuscular connections between the auricles and ventricles was demonstrated by Kent in 1914¹² and by Glomset and Glomset in 1940.⁷ In 1943, Wood, Wolferth, and Geckeler,²² through serial microscopic sections of the auriculoventricular groove, were able to identify a "Bundle of Kent" in the heart of an individual who, during life, showed the anomaly of a short P-R interval and a prolonged QRS complex with paroxysmal tachycardia.

The interesting experimental work of Butterworth and Poindexter^{1, 2} has added further weight to the theory that an accessory pathway is responsible for the phenomena observed in this syndrome. By means of an electrical amplifier the impulses from the auricle were conducted to one ventricle before they were conducted to this ventricle normally through the auriculoventricular conduction system. This produced typical electrocardiographic tracings with a short P-R interval and QRS prolongation. Reversal of the electrical stimulus from ventricle to auricle resulted in auricular tachycardia.

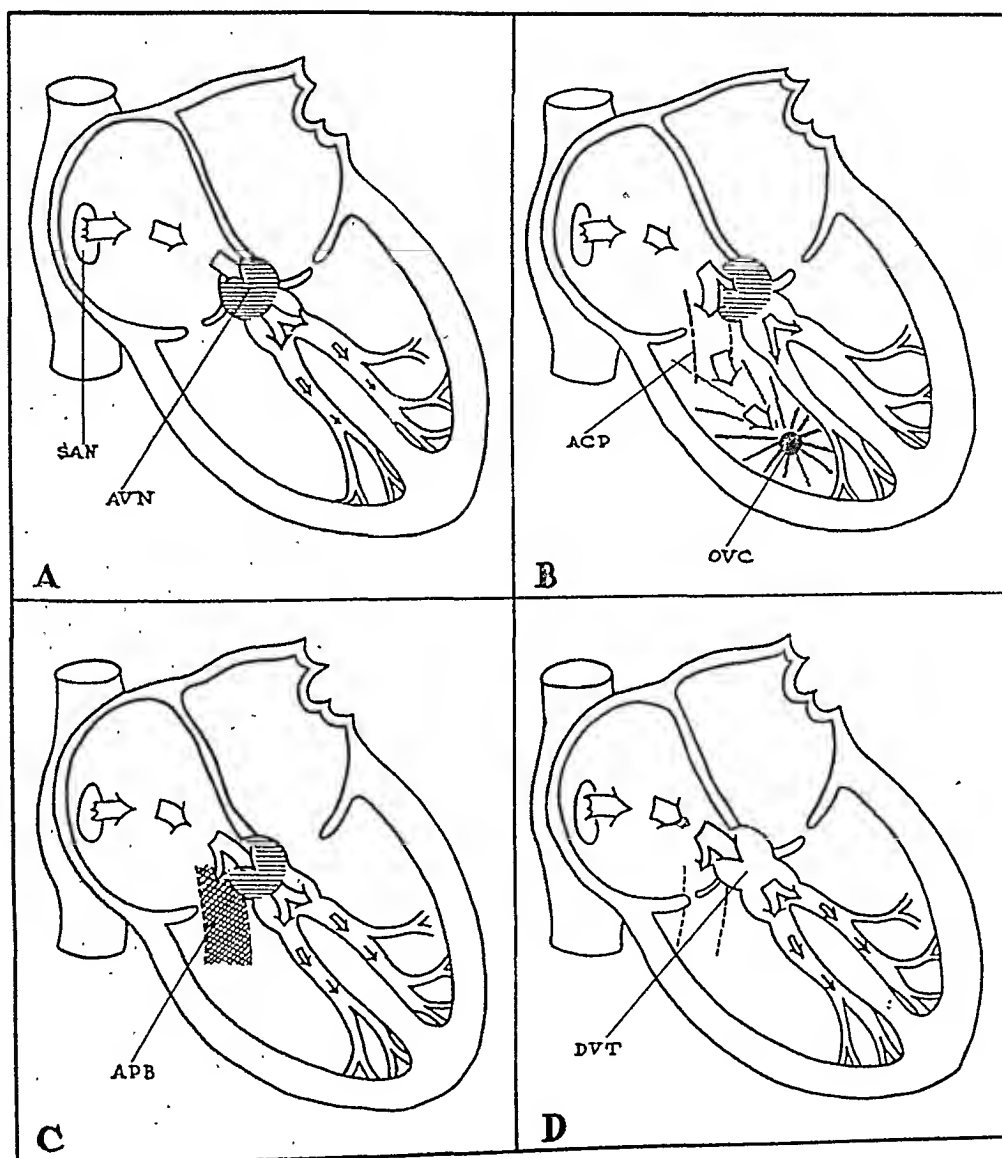
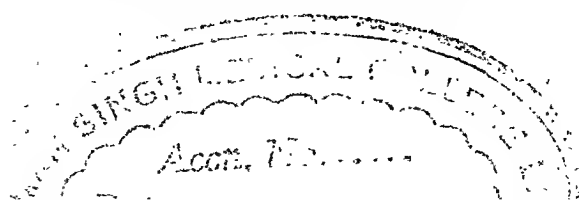


Fig. 1.—A, Diagrammatic representation of the normal origin and conduction of the cardiac impulse. SAN, sinoauricular node. AVN, auriculoventricular node, with normal delay indicated. B, Theoretical conduction in Wolff-Parkinson-White syndrome. ACP, accessory conduction pathway. OVC, origin of ventricular contraction. C, Condition which obtains with use of quinidine. APB, accessory pathway blocked. D, Condition present following the use of atropine. DVT, diminished vagus tone.

The simple hypothesis of an accessory A-V pathway has always left much to be desired in the explanation of the Wolff-Parkinson-White syndrome. With the study of "fusion beats" by Butterworth and Poindexter,³ we have an important contribution to the better understanding of the mechanisms involved. Their work supports the supposition that an auricular impulse may travel down



both the A-V bundle and an accessory pathway and result in a "fusion beat." The QRS configuration is determined by the degree of fusion which in turn is dependent upon the speed of conduction in each channel and the relative proximity of these channels to the initiating impulse. These authors demonstrated that the ventricle can be stimulated through the normal conduction system and by a second ventricular stimulus only during the short period (approximately 0.08 second) prior to the time the normal QRS complex would ordinarily appear.

It has been repeatedly pointed out that the Wolff-Parkinson-White syndrome occurs most commonly in young healthy adults. Many authors reporting instances in which myocardial damage was very likely or possibly present have made it a point to disregard or minimize that feature. In more recent years a few articles have appeared in which the presence of myocardial pathology is stressed.^{6, 8, 14} In reviewing our own cases and those in the literature we have been struck with the fact that no cases have been reported in infants, that a number of cases showing the Wolff-Parkinson-White syndrome have subsequently lost all evidence of it,^{19, 21} and that many published electrocardiograms indicate obvious myocardial disease. Though we are at a loss to explain the connection, it would appear that the presence of disease is more than a coincidence. Hunter and his associates¹¹ thoroughly reviewed the literature and found that, of ninety cases reported, eighteen had evidence of cardiac disease. They remarked that the syndrome undoubtedly could be produced by heart disease but pointed out that the presence of a short P-R interval with QRS distortion in no way influenced the prognosis. They noted that the syndrome was found associated with mitral stenosis, hypertension, aortic insufficiency (syphilitic and rheumatic), coronary thrombosis, and thyrotoxicosis. The oldest patient reported was 62 years of age. Wolferth and Wood¹⁹ reported the syndrome in a child of 14 who had a history of recurring paroxysmal tachycardia from the age of 2 years.

We are reporting nine cases that illustrate some of the variations encountered. They came to our attention during a period of one year in which approximately 3,600 electrocardiograms were reviewed.

REPORT OF CASES

CASE 1.—A 36-year-old white soldier came into the hospital on Dec. 2, 1944, because of shortness of breath and a "fluttering" sensation in the chest. There had been two previous episodes of dyspnea and tachycardia within the preceding three years, each lasting six to seven days. Although there was a history of some shortness of breath since childhood, this apparently did not interfere with his customary activities. The family and past history were noncontributory.

The heart was not enlarged. No murmurs were present. The heart rate was 120 at the wrist and approximately 130 at the apex. The rhythm was totally irregular. The lungs were clear. A soft mass, the size of a hazelnut, was noted in the left lobe of the thyroid. The examination was otherwise normal.

Vital capacity, circulation time, blood, urine, and x-ray studies of the heart were all normal. The basal metabolism was -10.

The patient was digitalized, and by the following morning the rhythm was regular with a rate of 86 per minute. The sounds were of good quality and no murmurs or thrills were noted. Digitalis was omitted the second day and, except when used experimentally later, was not again employed. During the two months that he was observed there were no other episodes of tachycardia or arrhythmia and no other cardiac symptoms.

Comment.—This was a case which demonstrated auricular fibrillation with persistence of the abnormal ventricular pattern indicating that the distribution was largely via the accessory pathway. It strongly resembles Case 1 of Levine and Beeson's¹³ series which was interpreted as ventricular tachycardia. During both spontaneous and induced (quinidine) reversion to normal distribution, T_2 and T_3 became sharply inverted resembling in appearance the curves seen in myocardial disease. Varying degrees of fusion could be produced with quinidine.

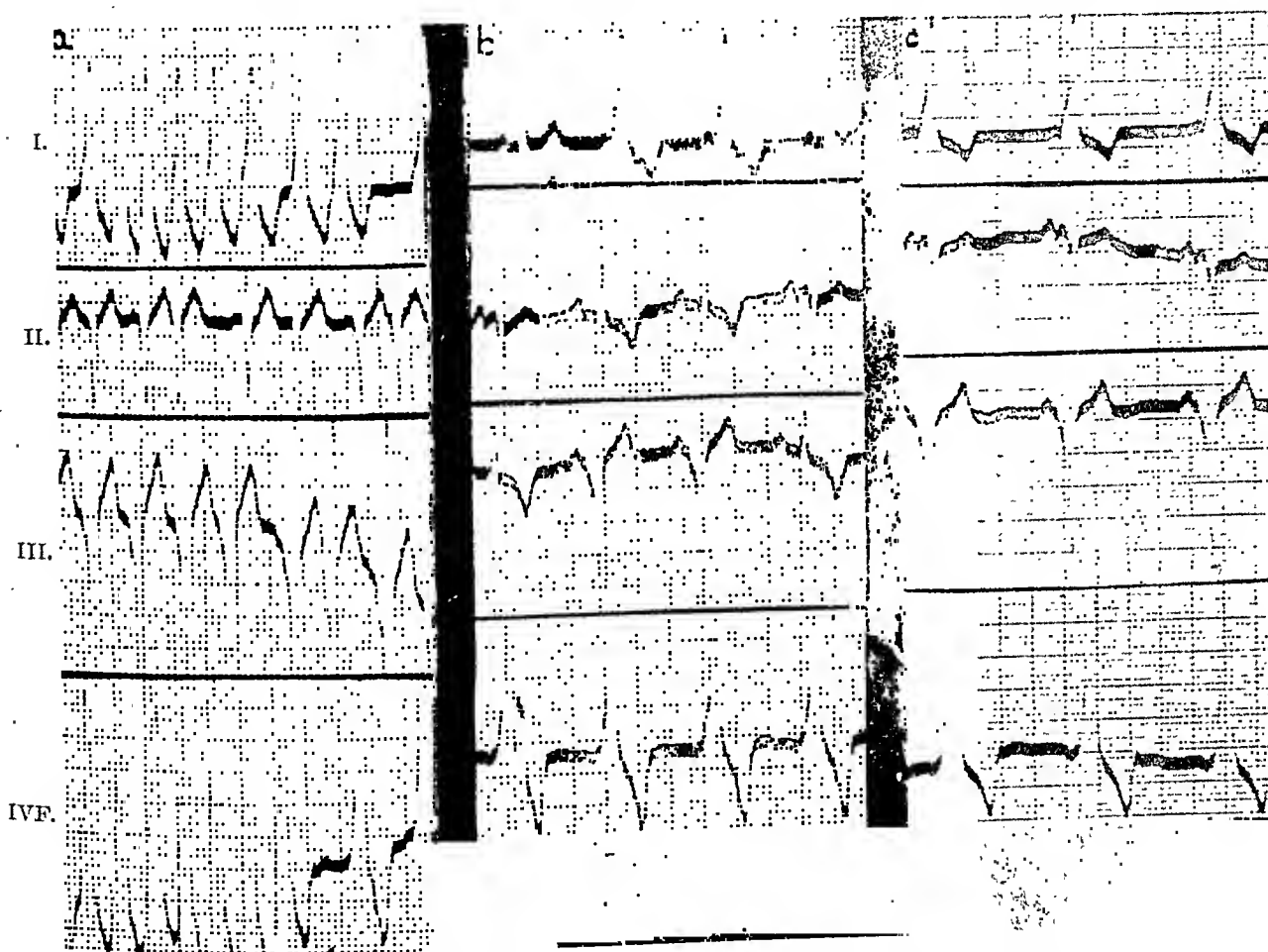


Fig. 2.—Case 1. *A*, Auricular fibrillation with a ventricular rate varying between 210 and 340 per minute. Duration of QRS approximately 0.12 second. Left axis deviation. *B*, This graph, made following cessation of tachycardia, demonstrates a mixture of normal and aberrant complexes. The normal complexes (Beats 1 and 4 in Lead I, Beats 2 and 3 in Lead II, and Beat 4 in Lead III) have a P-R interval of 0.16 second and a QRS duration of 0.06 second with an upright T_1 and sharply inverted T_2 and T_3 . The aberrant complexes have a P-R interval of 0.06 second and a QRS duration of 0.14 second and demonstrate left axis deviation. The P-S intervals of the normal and abnormal beats are identical. *C*, All of the complexes are typical of those seen in the Wolff-Parkinson-White syndrome. Measurements and contour of the complexes are essentially the same as those of the abnormal beats in *B*.

CASE 2.—A 26-year-old white soldier came into the hospital on March 11, 1945, with a complaint of "rapid beating of the heart." During the preceding three years he had been subject to fairly frequent episodes of typical paroxysmal tachycardia which required no treatment. When seen by the admitting officer, the pulse was found to be between 170 and 180 per minute, but by the time an electrocardiogram was made the rate was well within normal limits.

Physical examination revealed a healthy looking young man who was completely comfortable. The heart was entirely normal on examination. X-ray films of the chest showed no evidence of cardiac enlargement. The vital capacity, circulation time, and all cardiac function tests were normal. While under observation the patient had no cardiac complaints nor did he experience any further attacks of tachycardia.

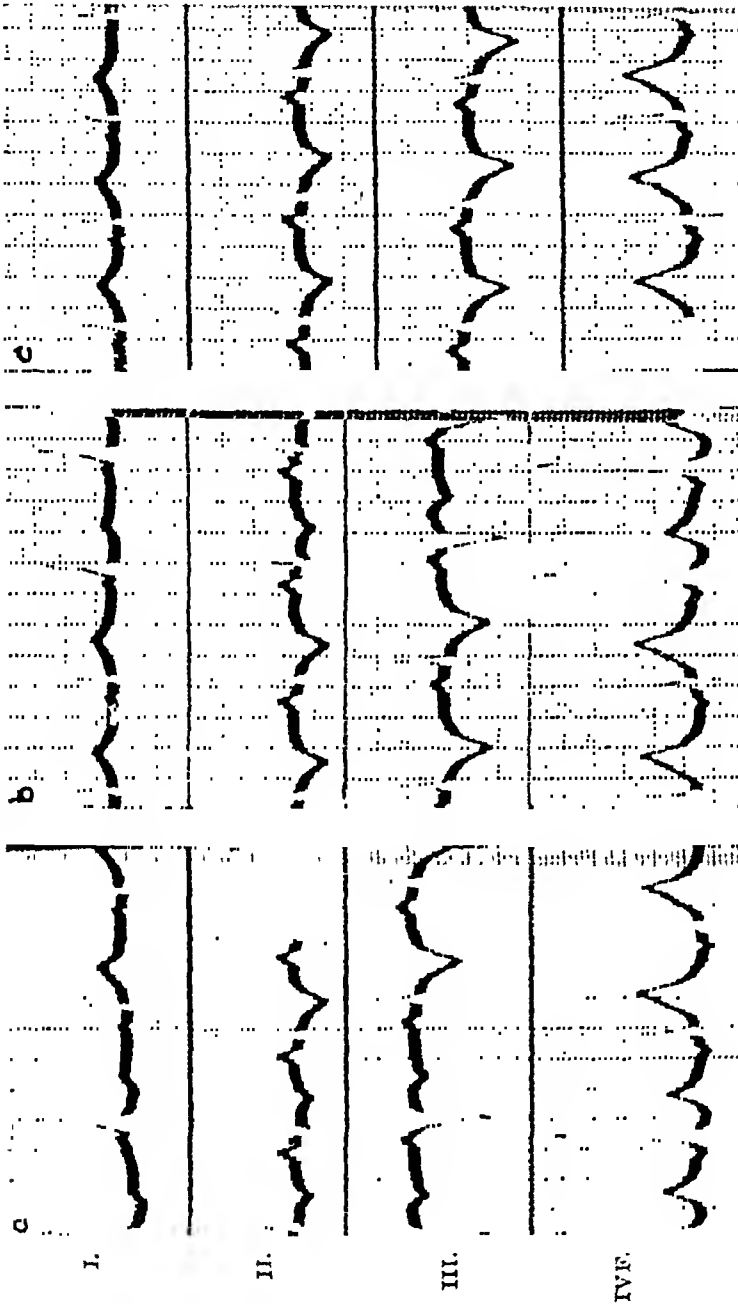


Fig. 3.—Case 1. A, This curve was obtained during the administration of quinidine (24 grains in two and one-half hours) and demonstrates not only a change to comparatively normal complexes but also an intermediate form (Beats 1 and 2 in each lead) first noted after the administration of small doses of the drug. In these beats the short P-R, long QRS relationship is maintained but alterations have occurred in the T waves and in QRS. These beats are transitional in character and probably represent varying degrees of fusion. The third and fourth beats in each lead indicate normal conduction and are essentially the same as those in C which occurred spontaneously. B, This tracing demonstrates the inherent instability of the state produced by inadequate quinidine dosage. Reversion to abnormal conduction is noted in Beats 3 and 4 of each lead. C, This tracing is representative of results obtained at will in Case 1 by adequate quinidine dosage. The P-R intervals are 0.16 second and the QRS complexes are 0.07 second in duration. T₂ and T₃ are inverted. The axis is normal.

Comment.—Although no paroxysmal tachycardia was recorded, this appears to be a typical case of the Wolff-Parkinson-White syndrome. Normal conduction could be obtained with quinidine, and intermediate forms were recorded with atropine and atropine with exercise.

CASE 3.—A 32-year-old white soldier was admitted on Jan. 2, 1945, with complaints of diarrhea and abdominal pain. There were no cardiac symptoms.

Physical examination was entirely unremarkable with the exception of some evidence of moderate weight loss and dehydration. The heart was within normal limits. An x-ray film of the heart was normal. All cardiac function studies were normal. Stool examination revealed trophozoites of *Endamoeba histolytica* and the diagnosis of amebic dysentery was made. Before beginning treatment with emetine, an electrocardiogram was made and found to be abnormal (Fig. 5a).

During the period of hospitalization this patient exhibited no paroxysmal tachycardia and had no cardiac complaint of any character.

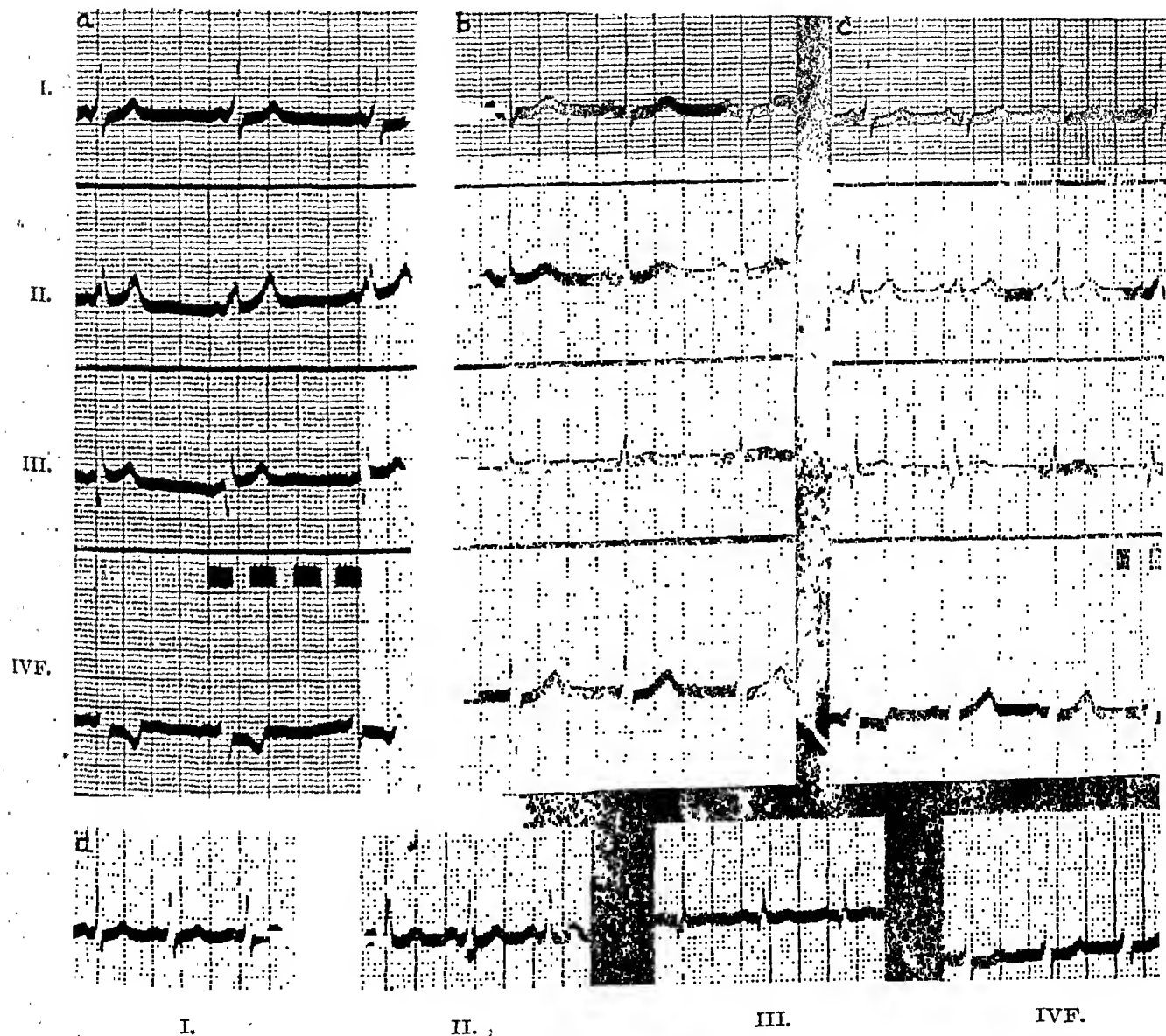


Fig. 4.—Case 2. *A*, Obtained on admission. P-R intervals 0.08 second. QRS duration 0.12 second. Slurring of the initial stroke of the QRS wave. Deep Qs. Left axis deviation. *B*, Recorded after the administration of quinidine (24 grains in six hours). P-R intervals 0.14 second. QRS duration 0.07 second. Normal axis. *C*, Made after the intravenous administration of atropine ($\frac{1}{32}$ grain). Some of the complexes (the first beat in Lead I, all beats in Lead II, Beats 1 and 2 in Lead III and Beat 1 in Lead IV) are intermediate between those demonstrated in *A* and *B* and represent varying degrees of fusion. P-R 0.10 second. QRS 0.10 second. Axis normal. T₄ diphasic. *D*, Made after intravenous atropine and exercise. Except for the rate this curve is very similar to *B*. However, note upright P_s (inverted in other tracings).

Comment.—This patient never had paroxysmal tachycardia or any other cardiac complaint. Although varying degrees of “fusion” could be produced with the administration of quinidine and atropine, the electrocardiographic pattern could not be brought back to normal.

CASE 4.—A 29-year-old soldier came into the hospital on Dec. 6, 1944, with a complaint of attacks of rapid heart action accompanied by shortness of breath. He had been receiving antisyphilitic therapy. Because of a positive spinal fluid Wassermann, he was transferred to an appropriate installation for definitive treatment, but was returned to the original station because of an abnormal electrocardiogram.

Physical examination was not remarkable. The heart was not enlarged, the rate was moderate, the rhythm was regular, and the sounds were good. No murmurs or thrills were noted. The lungs were clear and resonant throughout, and the reflexes were normal. All laboratory studies and cardiac function tests were within normal limits.



Fig. 5.—Case 3. A, Obtained on admission. P-R, 0.08 second. QRS, 0.14 second. Left axis deviation. B, Taken after the administration of quinidine (24 grains in three hours). P-R and QRS are difficult to measure but are probably not appreciably altered. There is a change in the axis with the appearance of a large R_2 and a small R_3 and diminution in the depth of S_2 . T_1 is higher, T_2 is lower, and T_3 is inverted. A large T_4 is noted. C, Recorded following the administration of atropine.

The patient continued to receive antisyphilitic therapy while on the cardiac ward. Six or seven hours after one such treatment he complained of a fluttering sensation in the chest and of breathlessness. This attack persisted for about one hour and toward its conclusion it was noted that the pulse was irregular.

During the two months that this soldier was under observation there were no instances of definite paroxysmal tachycardia and no cardiac symptoms.

Comment.—The tachycardia in this case is rather slow to be considered paroxysmal in character. Furthermore, the short P-R, wide QRS relationship persists. The significance of this is not clear.

Of considerable interest is the appearance of normal QRS complexes following sinus pauses. This is taken to indicate that since these ventricular com-

plexes were the result of impulses originating in or in the close vicinity of the A-V node, transmission distal from that point was in a normal fashion and did not involve the accessory pathway.

CASE 5.—A 37-year-old white soldier was hospitalized on May 23, 1945, because of frequent attacks of rapid heart action during the three weeks prior to his admission. The

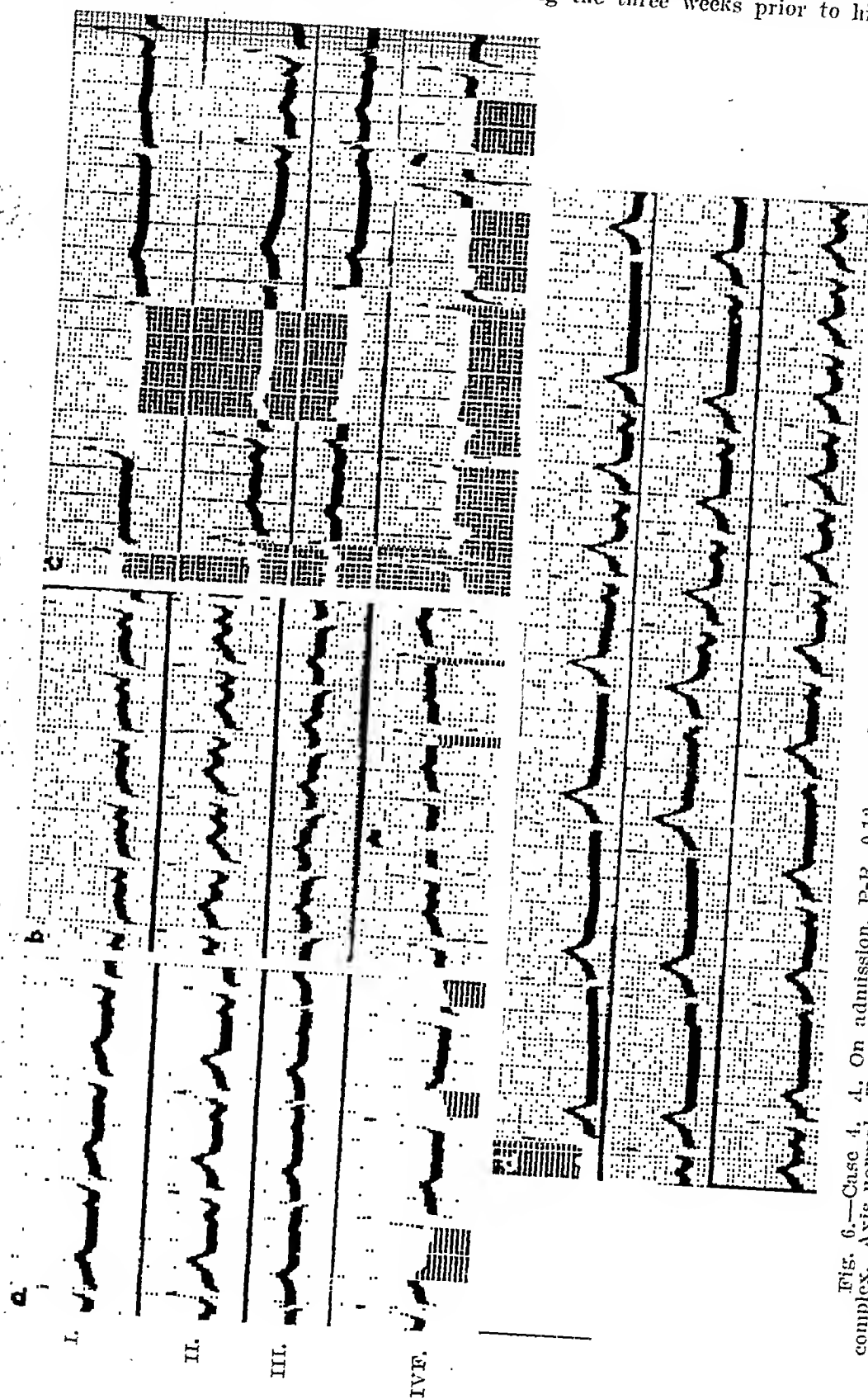


Fig. 6.—Case 4. A, On admission, P-R, 0.12 second, QRS, 0.13 second. Slurring of the initial limb of the QRS complex. Axis normal. T waves upright in all leads. B, Taken after the administration of mapharsen. Rate 130. P-R, 0.10 second. QRS, 0.12 second. Appearance of deep Qs. Left axis deviation. Diminution in height of T₁ and T₂. P-R, following quinidine. Note inversion of T₁ and T₂ with changes in rhythm and conduction. QRS complexes of normal contour and duration (0.07 second) are observed following periods of sinus pauses. C, All are Lead II, obtained during an interval of irregularity that followed the administration of mapharsen. There are periods of sinus pauses with nodal escape similar to those noted in C.

first attack came on suddenly three years earlier. Greater physical activity encountered in the Army was apparently responsible for the increasing frequency of the episodes. There were no other cardiac symptoms and no complaints of any kind between attacks of tachycardia.

Physical examination was entirely unremarkable with the exception of a soft systolic murmur which was best heard over the apex. The pulse was slow and regular. The heart was not enlarged. The lungs were clear. All the laboratory procedures and cardiac function tests were found to be normal.

Following a long period of observation, we were able to obtain a tracing during a paroxysm of tachycardia. This was controlled by breath holding.

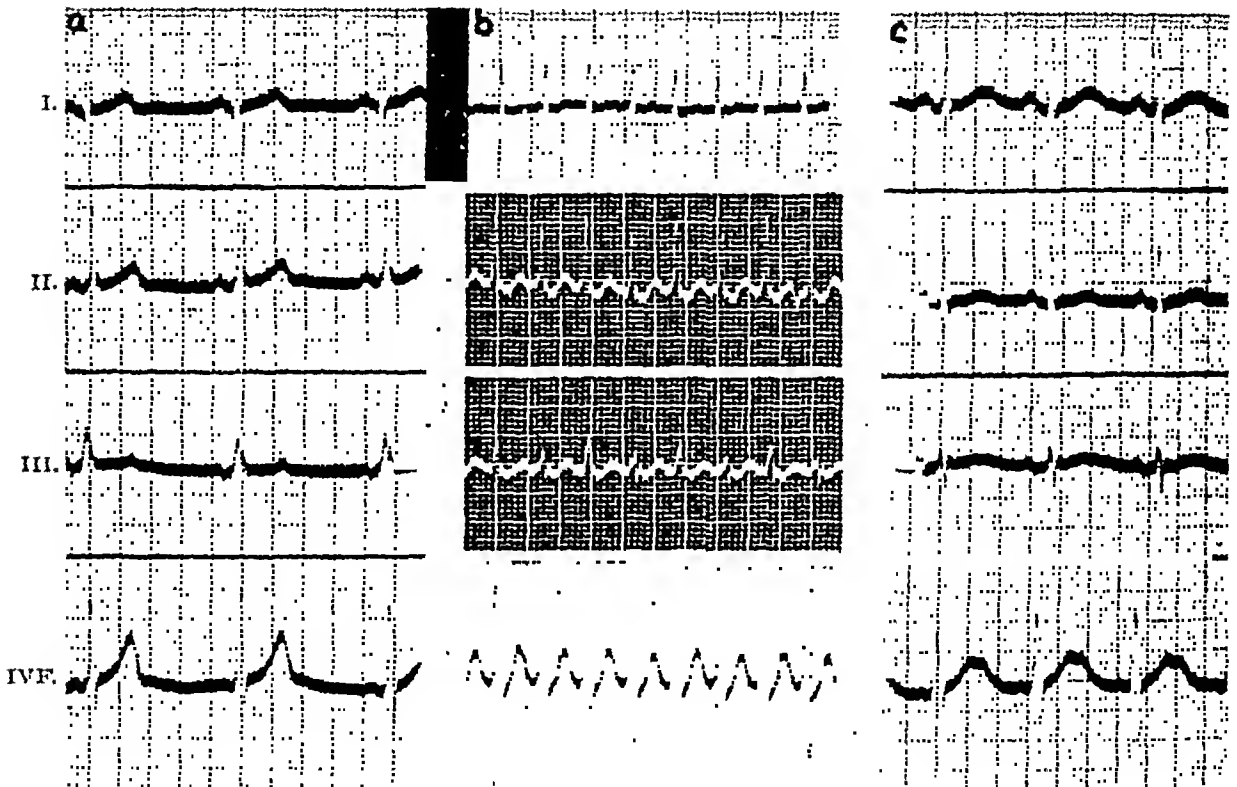


Fig. 7.—Case 5. *A*, Obtained on admission. P-R, 0.10 second. QRS, 0.12 second. Axis normal. *B*, Obtained during a paroxysm of tachycardia. Rate 210. Rhythm probably paroxysmal nodal tachycardia. P waves are not identifiable. QRS, 0.06 second. Axis essentially unaltered. Electrical alternans noted. *C*, Made following administration of quinidine (24 grains in three hours). P-R, 0.14 second. QRS, 0.08 second. Slight left axis deviation. T waves lowered, rounded, prolonged, and notched due to quinidine effect.

Comment.—The diagnosis in this case was obscure because accurate measurement was difficult. Additionally, the axis was normal. The use of quinidine produced changes which were definite though not spectacular. The record obtained during the paroxysm of tachycardia confirms the diagnosis. Rather marked electrical alternans appeared during the tachycardia.

CASE 6.—A 30-year-old soldier came into the hospital on June 12, 1945, with the complaint that his heart occasionally “skipped a beat.” On rare occasions, ever since childhood, he also is said to have had short periods of rapid heart action. The only other complaint referable to the heart was that of dyspnea on moderate exertion. During a previous hospitalization a diagnosis of heart block was said to have been made.

On physical examination the heart was not enlarged, the rate was moderate, the rhythm was regular, and the sounds were good. No murmurs or thrills were noted. A rare extrasystole was observed. X-ray films of the chest were normal and all cardiac function tests and laboratory procedures were within normal limits.

During the period of hospitalization there were no episodes of tachycardia and no cardiac symptoms.

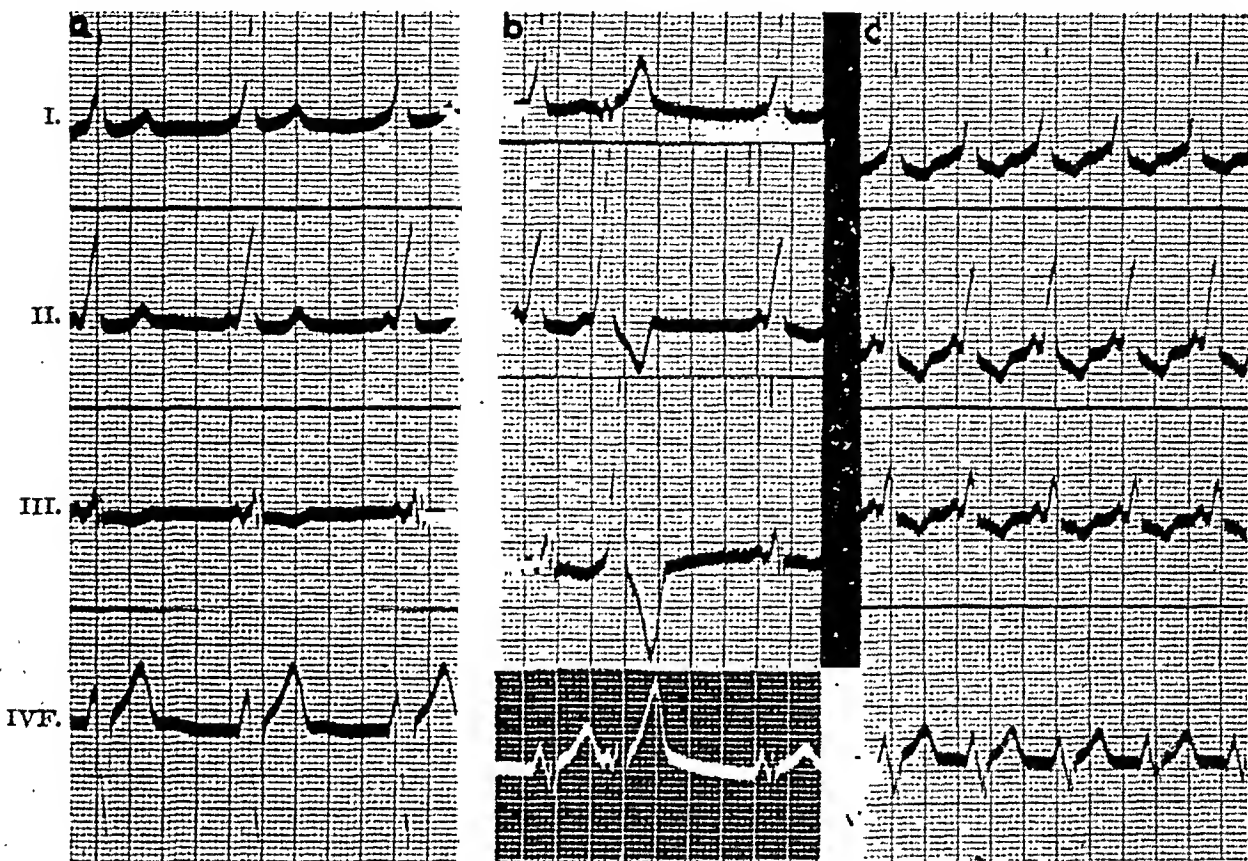


Fig. 8.—Case 6. *A*, Recorded on admission. P-R, 0.08 second. QRS, 0.16 second. Initial deflection of R wave is slurred. Axis normal. *B*, Ventricular extrasystoles are present. Premature beats were never observed except following exercise and were always associated with depression or inversion of the T waves in the limb leads. *C*, This tracing was obtained following vigorous exercise. Rate, 116. P-R, 0.10 second. QRS, 0.10 second. T waves sharply inverted in all limb leads and S-T segments slightly depressed. There is diminution in the size of all waves in Lead IV.

Comment.—This case is of interest in that ventricular premature beats were recorded. They occurred following slight exercise and were abolished during greater activity.

The same case presented a phenomenon which to us is without adequate explanation. Electrocardiograms made following brisk exercise always demonstrated inversion of the T waves in the limb leads and diminution in height of all the waves in Lead IV. There was also a slight increase in the P-R interval and a shortening of the duration of the QRS complex.

CASE 7.—A 28-year-old white soldier entered the hospital complaining of a generally tired-out and run-down feeling. The family and past history were noncontributory. Approximately six years earlier, he was examined for life insurance and hypertension was noted. He tired rather easily on moderate effort and suffered from occasional occipital headaches. There was no dyspnea on exertion nor precordial distress and no edema of the extremities was ever noted.

Physical examination was not remarkable. The heart was not enlarged, the rate was moderate, the rhythm was regular, and the sounds were of good quality. No murmurs or thrills were noted. The blood pressure was 150/92. X-ray films of the heart demonstrated no enlargement or distortion. The lungs were normal. The serology was negative and all other laboratory findings were normal. The cardiac function tests were normal.

During his hospitalization the patient did not have any tachycardia nor were there any other complaints referable to the heart.

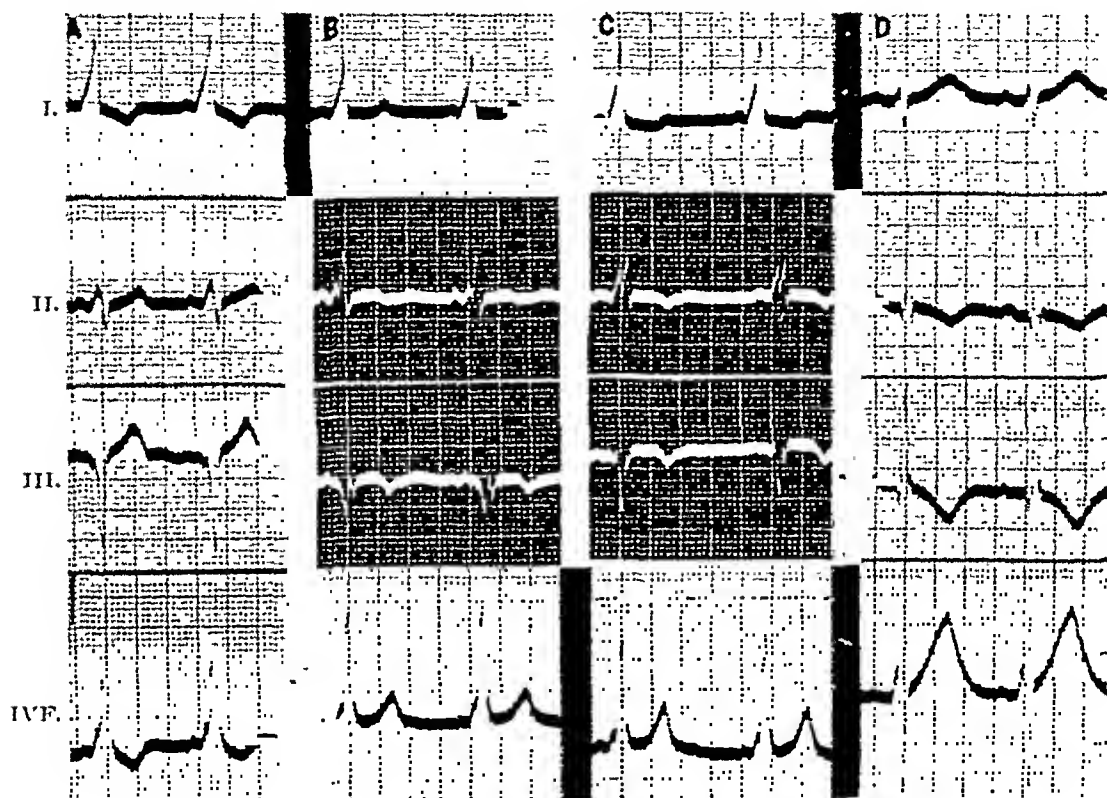


Fig. 9.—Case 7. A, Recorded on admission. P-R, 0.10 second. QRS, 0.14 second. Left axis deviation. The T waves are inverted in Leads I and IV, and upright in Leads II and III. B, This tracing was obtained several hours after that shown in A, and under identical circumstances. P-R and QRS durations are unchanged. There is marked alteration in the appearance of QRS complexes of Leads II and III. RS-T₁ is somewhat depressed. T₁ is upright, T₂ is diphasic, and T₃ is inverted with rounded and slightly elevated RS-T segments. T₄ has become erect. C, This tracing was obtained under the same conditions that obtained in A and B. No medication had been given. Duration of P-R and QRS unchanged. Configuration of QRS₂ has altered. T₁ is diphasic, and T₂ and T₃ are inverted. RS-T₄ is elevated. Lead IV is unchanged. D, This tracing was made approximately one hour after the administration of 33 grains of quinidine. P-R, 0.18 second. QRS, 0.10 second. There is slight right axis deviation with a small R₁ and prominent S₁. The T waves are all large and rounded. T₁ is upright, T₂ and T₃ are sharply inverted. QRS₄ has acquired a deep S wave while the height of the R wave has decreased. This tracing strongly resembles that obtained in Case 1 by similar means (Fig. 3, C).

Comment.—This patient is of considerable interest because of the marked alterations in the appearance of the ventricular component which occurred spontaneously and under unvarying circumstances. This change cannot be explained on the basis of altering degrees of fusion because the P-R intervals and the QRS duration remain constant and unchanged. The only satisfactory explanation which can support these findings is that of *multiple accessory pathways*.¹⁷ Under such circumstances, variation in the number and/or combinations of such channels acting over a given interval could effectively alter the distribu-

tion of the impulse and, with it, the character of the ventricular complex. The factors tending to influence the selection of abnormal pathways are quite beyond our knowledge at the present time. However, they may be susceptible to experimental analysis similar to that employed by Butterworth and Poindexter.³

Administration of 33 grains of quinidine over a period of two hours produced characteristic alteration in the appearance of the tracing with reversion to physiologic conduction.

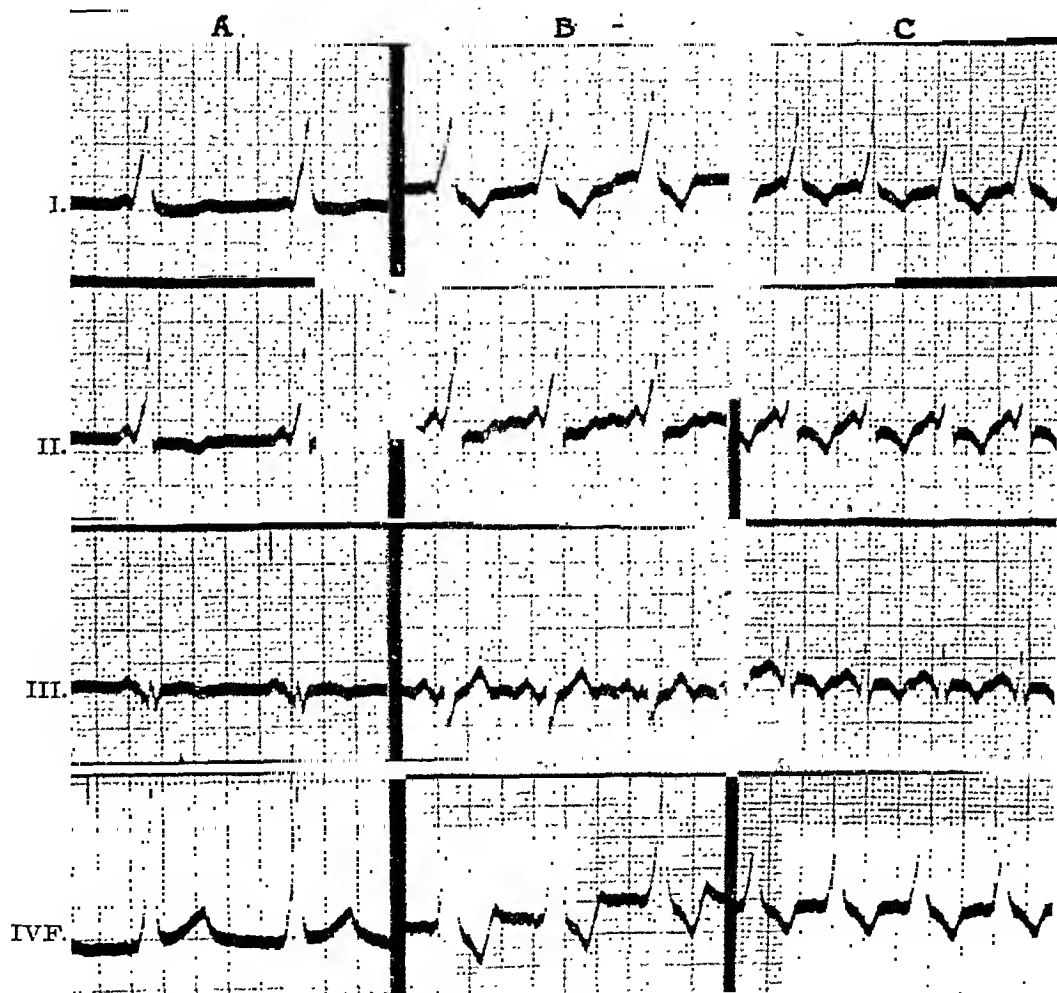


Fig. 10.—Case 8. *A*, Obtained on admission. P-R, 0.08 second. QRS 0.14 second. *B*, Recorded following moderate exercise. Note marked change in the T waves and in the RS-T segments. There is also a shift of the axis toward the left. *C*, Obtained following the intravenous administration of atropine and subsequent exercise. All of the T waves are now inverted. The duration of the QRS complex has been diminished by approximately 0.02 second without a comparable increase in the P-R interval. The axis has rotated toward the right.

CASE 8.—A 26-year-old white soldier came into the hospital on Dec. 11, 1945, complaining of restlessness and rapid, irregular heart action. This occurred suddenly following a brisk run of some 50 yards. The admitting physician described a grossly irregular rhythm and noted a pulse deficit. An electrocardiogram was not made until the following morning at which time the arrhythmia had disappeared. The tracing demonstrated a normal rhythm with a configuration characteristic of the Wolff-Parkinson-White syndrome.

The attack for which the patient entered the hospital was his first. The history was otherwise noncontributory. The physical examination revealed only a soft systolic apical murmur. All of the routine laboratory tests, cardiac function tests, and chest x-rays were normal.

The use of quinidine did not alter the tracing significantly but exercise and exercise with atropine resulted in interesting changes.

During his hospitalization the patient had no further attacks of tachycardia and did not have any cardiac complaints.

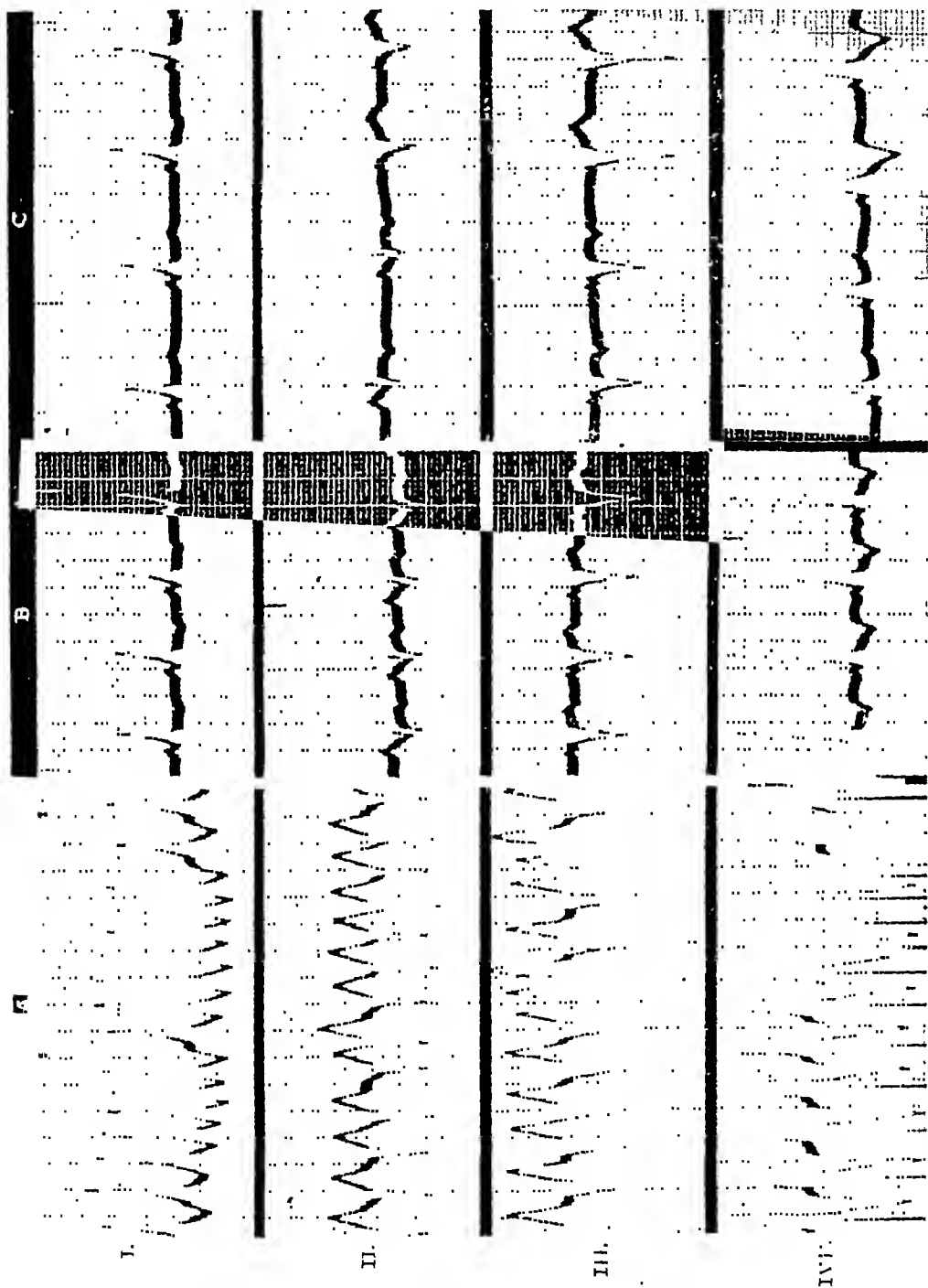


Fig. 11.—Case 9. A, Obtained on admission. Rhythm either auricular fibrillation with abnormal ventricular conduction or paroxysmal ventricular tachycardia with marked irregularity. Rate varies between 250 and 300. B, Recorded the morning following admission. P-R, 0.10 second. QRS, 0.12 second. Left axis deviation. C, This tracing was made several days after B. With each lead the patient began in the right lateral position and then turned to the supine. Several seconds and about five beats after the change of position an abrupt change in the appearance of the electrocardiogram occurred. Two beats are shown before and two after the change took place. Note that a change in axis has occurred toward the left and that all of the T waves have reversed their directions.

Comment.—The variations in the axis and in the T waves are probably the result of varying combinations of the several aberrant conduction pathways apparently present in this case. The shortening of the duration of the QRS complex without a like increase in the P-R interval, however, is without adequate explanation.

CASE 9.—A 20-year-old white man was admitted to the hospital on Dec. 18, 1945, with the complaint of rapid and irregular heart action. There was a history of two similar attacks, both following effort, during the preceding ten years. The history was not otherwise remarkable.

Physical examination revealed the presence of what was apparently auricular fibrillation. The heart was not otherwise unusual and no other abnormalities were observed. An electrocardiogram demonstrated what was either paroxysmal ventricular tachycardia with considerable irregularity or auricular fibrillation with bundle branch block and an exceedingly rapid ventricular rate.

The attack stopped spontaneously during the night and on the following morning the cardiac rate was moderate and the rhythm regular. An electrocardiogram at this time demonstrated a characteristic short P-R, long QRS relationship.

All of the customary laboratory studies were normal. X-ray of the chest and cardiac function tests were all within normal limits.

It was not possible to produce any significant alterations of the electrocardiogram by the use of exercise, atropine, or quinidine. However, a rather unusual electrocardiographic phenomenon was observed in this patient after he had changed his position from right lateral to supine. Several seconds after the change was completed there was an abrupt shift in axis and all of the T waves reversed their direction. That this was not due purely to the anatomic change in position is apparent when it is recalled that there was a delay of several seconds before the electrical change occurred.

Comment.—The tachycardia in this case is probably of the same type as that found in Case 1. It disappeared spontaneously. The immediate cause for the gross changes noted with alteration of anatomic position is not apparent. However, the mechanism is doubtless similar to that postulated in Cases 6, 7, and 8.

DISCUSSION

Several details of this condition merit somewhat further discussion and theory. It has usually been considered that the attacks of paroxysmal tachycardia so frequently associated with this syndrome are the result of impulse re-entry through the anomalous A-V bundle. Since most of the tachycardias recorded are of the supraventricular type with a normal QRS complex it is probable that the original impulse in such instances travels from the auricle down the normal A-V pathway and returns to the auricle through the aberrant channel. The inability of the "Kent bundle" to transmit retrograde impulses would explain the freedom from paroxysmal tachycardia noted in approximately 25 per cent of the reported cases.

In reviewing those cases which were considered to be ventricular tachycardia^{13, 16} it is felt that some of the electrocardiograms shown might have been interpreted as auricular fibrillation with a prolonged, distorted QRS similar to Cases 1 and 9 herein reported. In order to explain the wide, bizarre QRS complex, it is necessary to postulate that the path of distribution is largely through the accessory bundle. The cases of true ventricular tachycardia probably arise in the lower portion of the aberrant pathway.

An investigation of this subject by Rosenbaum and his co-workers¹⁷ recently appeared in the JOURNAL. We were interested to find that their deductions, arrived at through careful studies with unipolar leads from the esophagus, precordium, and other parts of the thorax, closely resemble the experimental con-

clusions of Butterworth and Poindexter.³ They do not employ the term "fusion beats" but conclude that "impulses" pass from the auricles to the ventricles not only by way of the atrioventricular node and His bundle but by "one or more additional channels." They also suggest that these pathways may be present but not functioning. These conclusions appear valid when applied to those cases showing a mixture of abnormal and physiologic complexes (Case 1) and where the abnormal complexes vary in appearance (Case 4).

If the presence of one or more conduction pathways is conceded, the pharmacologic action of quinidine and atropine become apparent. Quinidine by its depressant action on ectopic tissue is thought to delay conduction in the aberrant system thus permitting the impulse to progress down the normal pathway (Fig. 1, C). Atropine, on the other hand, by diminishing or abolishing normal or increased vagus control over the A-V conduction system makes the normal pathway the more favorable one and allows the impulse to take that route in preference to the accessory pathway (Fig. 1, D). One may liken the two (or more) pathways to competing electrical circuits having different and varying resistances, with the impulse mostly or wholly traversing the one with the least impedance.

Since the pharmacologic action of quinidine and atropine in this condition is apparently complementary, the one interfering with abnormal conduction and the other enhancing physiologic conduction, the two drugs were used simultaneously in those cases not altered by either drug separately. However, it was noted that where quinidine alone did not induce normal conduction the addition of the other drug resulted in no further change. The dose of quinidine required to produce physiologic conduction varied from 6 grains an hour for two or three doses to 33 grains in two hours (Case 7). Atropine in intravenous doses up to $\frac{1}{50}$ grain and atropine with exercise were also effective to a lesser degree. We were unable to obtain satisfactory results with digitalis even though large doses were employed. In Case 1 the rhythm changed from auricular fibrillation to normal either because of or in spite of digitalis.

It is interesting to note that in those cases where physiologic tracings were obtained following the use of quinidine (Cases 1, 2, and 5) the history indicated a fairly recent origin or paroxysmal tachycardia. In Case 7 changes were secured by similar means but this patient had no cardiac complaints. One may speculate that electrocardiographic reversal by pharmacologic means is more likely to occur in those cases where the aberrant mechanism is not one of long standing. In borderline cases it may be possible to employ quinidine as a diagnostic test.

The relationship of myocardial disease to the Wolff-Parkinson-White syndrome is, in our opinion, the major unexplained issue. It is generally admitted that the syndrome may be produced occasionally by heart disease. Case 1, which showed deep inversion of T_2 and T_3 when the conduction was physiologic suggests that myocardial disease may have had some part. This factor should not be lost sight of, and the nature of the cause, if it can be determined, should always be carefully considered in making a prognosis. A few attractive theories

have been advanced, but no conclusive evidence has been presented. Fox⁴ has suggested that a circulatory difficulty of the A-V node due to coronary sclerosis may sufficiently depress its functional activity to permit an already present ectopic mechanism to take over some of the conducting functions. Other inflammatory, toxic or degenerative processes could conceivably have a similar effect. It is our opinion that this phase of the problem has not been sufficiently emphasized or investigated.

SUMMARY AND CONCLUSION

1. Nine patients who showed the Wolff-Parkinson-White Syndrome are presented and a few of the variations encountered are discussed.

2. The various theories advanced in the explanation of the pathogenesis are referred to and an evaluation of their merits is attempted. In our opinion the most acceptable explanation is that which assumes the presence of one and frequently several accessory conduction pathways which result in "fusion beats."

3. The influence of quinidine, atropine, and exercise on the "short P-R, long and aberrant QRS" is discussed. In borderline cases these changes may be employed as a diagnostic test.

4. The relationship of myocardial disease to the Wolff-Parkinson-White syndrome is discussed. Several of the patients reported in this paper had systemic disease and two showed definite electrocardiographic abnormalities during periods of normal conduction.

REFERENCES

1. Butterworth, J. S., and Poindexter, C. A.: Short P-R Interval Associated With a Prolonged QRS Complex. A Clinical and Experimental Study, *Arch. Int. Med.* 69: 1437, 1942.
2. Butterworth, J. S.: The Experimental Production of the Syndrome of Apparent Bundle Branch Block With Short P-R Interval, *J. Clin. Investigation* 20: 458, 1941.
3. Butterworth, J. S., and Poindexter, C. A.: Fusion Beats and Their Relation to the Syndrome of Short P-R Interval Associated With a Prolonged QRS Complex, *AM. HEART J.* 28: 149, 1944.
4. Fox, T. T.: Aberrant Atrioventricular Conduction in a Case Showing a Short P-R Interval and an Abnormal but Prolonged QRS Complex, *Am. J. M. Sc.* 209: 199, 1945.
5. Fox, T. T., Travell, J., and Molofsky, L.: Action of Digitalis on Conduction in the Syndrome of Short P-R Interval and Prolonged QRS Complex, *Arch. Int. Med.* 71: 206, 1943.
6. Franke, H., and Vetter, R.: Beitrage zur Pathogenese der Herzstrom Kurven mit Verkürzter, Vorhof Kammer-Distanz und mit Verbreiteter Anfangsschwankung, *Arch. Kreislaufforsch.* 11: 283, 1943.
7. Glomset, D. J., and Glomset, A. T.: A Morphologic Study of the Cardiac Conduction System in Ungulates, Dog, and Man, *AM. HEART J.* 20: 389, 1940.
8. Granpera, E., and Govia, J.: Nueva Teoria Patogenica del Sindrome de Wolff, Parkinson y White, *Vida Nueva* 52: 272, 1943.
9. Hamburger, W. W.: Bundle Branch Block. Four Cases of Intraventricular Block Showing Some Interesting and Unusual Clinical Features, *M. Clin. North America* 13: 343, 1929.
10. Holzmänn, M., and Scherf, D.: Ueber Elektrokardiogramme mit verkürzter Vorhof-Kammer-Distanz und positiven P-Zacken, *Ztschr. f. klin. Med.* 121: 404, 1932.
11. Hunter, A., Papp, C., and Parkinson, J.: The Syndrome of Short P-R Interval, Apparent Bundle Branch Block and Associated Paroxysmal Tachycardia, *Brit. Heart J.* 2: 107, 1940.

12. a. Kent, A. F. S.: Proceedings of Physiol. Soc., Nov. 12, J. Physiol., 1892.
b. Idem: The Structure of the Cardiac Tissues at the Auriculoventricular Junction, J. Physiol. 47: 17, 1913.
c. Idem: Observations on the Auriculoventricular Junction of the Mammalian Heart, Quart. J. Exper. Physiol. 7: 193, 1913.
d. Idem: The Right Lateral Auriculoventricular Junction of the Heart, J. Physiol. 48: 22, 1914.
e. Idem: A Conducting Path Between the Right Auricle and External Wall of the Right Ventricle in the Heart of a Mammal, J. Physiol. 48: 57, 1914.
f. Idem: Illustrations of the Right Lateral Auriculoventricular Junction in the Heart, J. Physiol. 48: 63, 1914.
13. Levine, S. A., and Beeson, P. B.: The Wolff-Parkinson-White Syndrome, With Paroxysms of Ventricular Tachycardia, AM. HEART J. 22: 401, 1941.
14. Mahaim, I.: Le Syndrome de Wolff-Parkinson-White et sa Pathogénie, Helvet. med. acta. 8: 483, 1941.
15. Movitt, E. R.: Some Observations on the Syndrome of Short P-R Interval With Long QRS, AM. HEART J. 29: 1, 1945.
16. Palatucci, O. A., and Knighton, J. E.: Short P-R Interval Associated With Prolongation of QRS Complex; A Clinical Study Demonstrating Interesting Variations, Ann. Int. Med. 21: 58, 1944.
17. Rosenbaum, F. F., Hecht, H. H., Wilson, F. N., and Johnston, F. D.: The Potential Variations of the Thorax and the Esophagus in Anomalous Atrioventricular Excitation (Wolff-Parkinson-White Syndrome) AM. HEART J. 29: 281, 1945.
18. Wilson, F. N.: A Case in Which the Vagus Influenced the Form of the Ventricular Complex of the Electrocardiogram, Arch. Int. Med. 16: 1008, 1915.
19. Wolferth, C. C., and Wood, F. C.: The Mechanism of Production of Short P-R Intervals and Prolonged QRS Complexes in Patients With Presumably Undamaged Hearts; Hypothesis of an Accessory Pathway of Auriculoventricular Condition (Bundle of Kent) AM. HEART J. 8: 297, 1933.
20. Wolferth, C. C., and Wood, F. C.: Further Observation on the Mechanism of the Production of a Short P-R Interval in Association With Prolongation of the QRS Complex, AM. HEART J. 22: 450, 1941.
21. Wolff, L., Parkinson, J., and White, P. D.: Bundle Branch Block With the Short P-R Interval in Healthy Young People Prone to Paroxysmal Tachycardia, AM. HEART J. 5: 685, 1930.
22. Wood, F. C., Wolferth, C. C., and Geckeler, G. D.: Histologic Demonstration of Accessory Muscular Connections Between Auricle and Ventricle in a Case of Short P-R Interval and Prolonged QRS Complex, AM. HEART J. 25: 454, 1943.

Clinical Reports

TRANSIENT VENTRICULAR FIBRILLATION

REPORT OF A CASE WITH SPONTANEOUS RECOVERY

WALTER T. ZIMDAHL, M.D., AND FRANK T. FULTON, M.D.
PROVIDENCE, R. I.

IT HAS been fairly well recognized in recent years that cardiac syncope may result from transient ventricular standstill or ventricular fibrillation. Ventricular fibrillation in man is often a terminal event in various forms of cardiac failure, particularly sudden occlusion of the coronary vessels.^{1, 2} It has been shown by several investigators,³⁻⁹ particularly Schwartz and Jezer,⁶ that ventricular fibrillation may occur as a transient disorder from which the patient may recover. Until the studies of these authors, little was known of the clinical manifestations of this disorder.

Schwartz⁴ pointed out that the periods of unconsciousness in patients with auriculoventricular dissociation are associated with transient seizures of ventricular fibrillation much more commonly than had been suspected. He called attention to the fact that the clinical diagnosis of transient ventricular fibrillation may be suspected in such patients if, preceding a period of unconsciousness, the heart rate has been noted to increase above the usual basic rate. Schwartz and Jezer⁶ also presented a patient in which certain premonitory disturbances preceded a transient seizure of ventricular fibrillation. One such disturbance consisted of alternate premature beats of the ventricles, which increased the basic ventricular rate. These were followed shortly by irregular periods of recurring groups of aberrant ventricular oscillations, of which only the first few could be heard at the apical region of the heart or felt at the radial pulse. Borg and Johnson⁷ presented a case of ventricular standstill which had had an arrhythmia similar to that described as a prefibrillatory mechanism. They suggested that the clinical diagnosis of this disturbance is probably impossible without electrocardiographic records.

Most of the patients described by these authors had A-V heart block in some form. The number of such cases which have been described is comparatively small and we feel it worth while to report another case.

CASE REPORT

J. H., a 66-year-old white man, was admitted to the Rhode Island Hospital, May 8, 1945, because of "convulsions." Except for scarlet fever in childhood there was no history of previous illness.

From the Heart Station of the Rhode Island Hospital, Providence, R. I.
Received for publication June 24, 1945.

Two weeks before admission he did not feel well and rested for one day. Three days before admission he developed an illness characterized by chills without cough, which his physician diagnosed as "pneumonia," and for which he was given full doses of sulfadiazine. He progressed favorably and felt well. Four hours before admission he was found on the floor of his bathroom. He was very cyanotic and had generalized twitchings from which he recovered in a short time. Three additional seizures occurred before he reached the hospital.

Soon after admission the patient suddenly became extremely cyanotic, apneic, and pulseless. Oxygen and coramine were administered immediately. Because of the absence of pulse and apical sounds and because of the marked cyanosis, ventricular standstill was considered to be the cause of the syncope. He was given 0.1 Gm. of Metrazol subcutaneously every five minutes, for a total of 0.6 Gm. The blood pressure at this time was not obtainable. The patient gradually lost his cyanosis, became flushed, and then regained his normal color.

Examination between attacks revealed that the patient was a well-developed, rather obese man who was clearly oriented. The blood pressure was 120/90; the rectal temperature, 101.6° F.; respirations, 30; and the pulse rate, 120 per minute. The pulse, initially irregular, gradually became regular. The lungs revealed diminution of breath sounds at the left base and a few crepitant râles. The heart was enlarged to the left and no murmurs were audible. The peripheral vessels were sclerotic.

Electrocardiogram taken at this time (Fig. 1, Column 1) showed a ventricular rate of 80 per minute with a regular sinus rhythm and right bundle branch block.

A few minutes after the tracing was taken the patient suddenly became pale, closed his eyes, and manifested general twitching, following which his eyes opened and he appeared motionless. At this time no pulse or apical heart sound could be heard. His respirations increased to 40. The patient was unconscious and his face was purplish. The inspiratory phase became almost double the expiratory phase and the breathing was noted to be stertorous. He again developed a short convulsive seizure which involved the whole body during which his eyes rolled irregularly to the left and upward. Two minutes later the respirations stopped; he became intensely cyanotic and appeared lifeless. This episode lasted for a period of one minute. Spontaneous revival was associated with the return of the heartbeat and respirations.

Upon regaining full consciousness he was incoherent and confused but within a few minutes became rational and asked, "Did I have another?"

During this period of syncope which lasted about five minutes, he was incontinent of urine.

Within a period of eight hours, the patient had fifteen such attacks, each lasting approximately two to six minutes. An electrocardiogram taken during one of these attacks is shown in Fig. 2. After the fifteenth seizure the patient remained asymptomatic and rested comfortably.

Following his last seizure, the patient was given 0.2 Gm. of quinidine sulfate orally every four hours. This was continued for ten days following which the dosage was gradually reduced to 0.2 Gm. every twelve hours. On the twenty-third day, the drug was discontinued. After he had been free of all symptoms for thirty-seven days, he was discharged from the hospital.

ELECTROCARDIOGRAMS

Fig. 1, Column 2, shows the electrocardiogram taken May 9, 1945. It shows sinus rhythm, a rate of 76, A-V conduction time of 0.20 second, and right bundle branch block. There is marked slurring of the QRS complexes. The T waves are upright in Leads I and II, slightly inverted in Lead III, and diphasic in CF₄.

A record taken May 11, three days later (Column 3), shows T-wave changes in all leads. These waves are flattened in Lead I, smaller in Lead II, upright and small in Lead III, and inverted in CF₄. The marked slurring of the QRS complex has disappeared.

A record taken May 15, four days later (Column 4), shows further changes. These changes suggest that the patient had marked coronary artery disease and that an acute myocardial infarction had initiated his syncopal attacks. Further serial records confirmed this diagnosis.

1.

2.

3.

4.

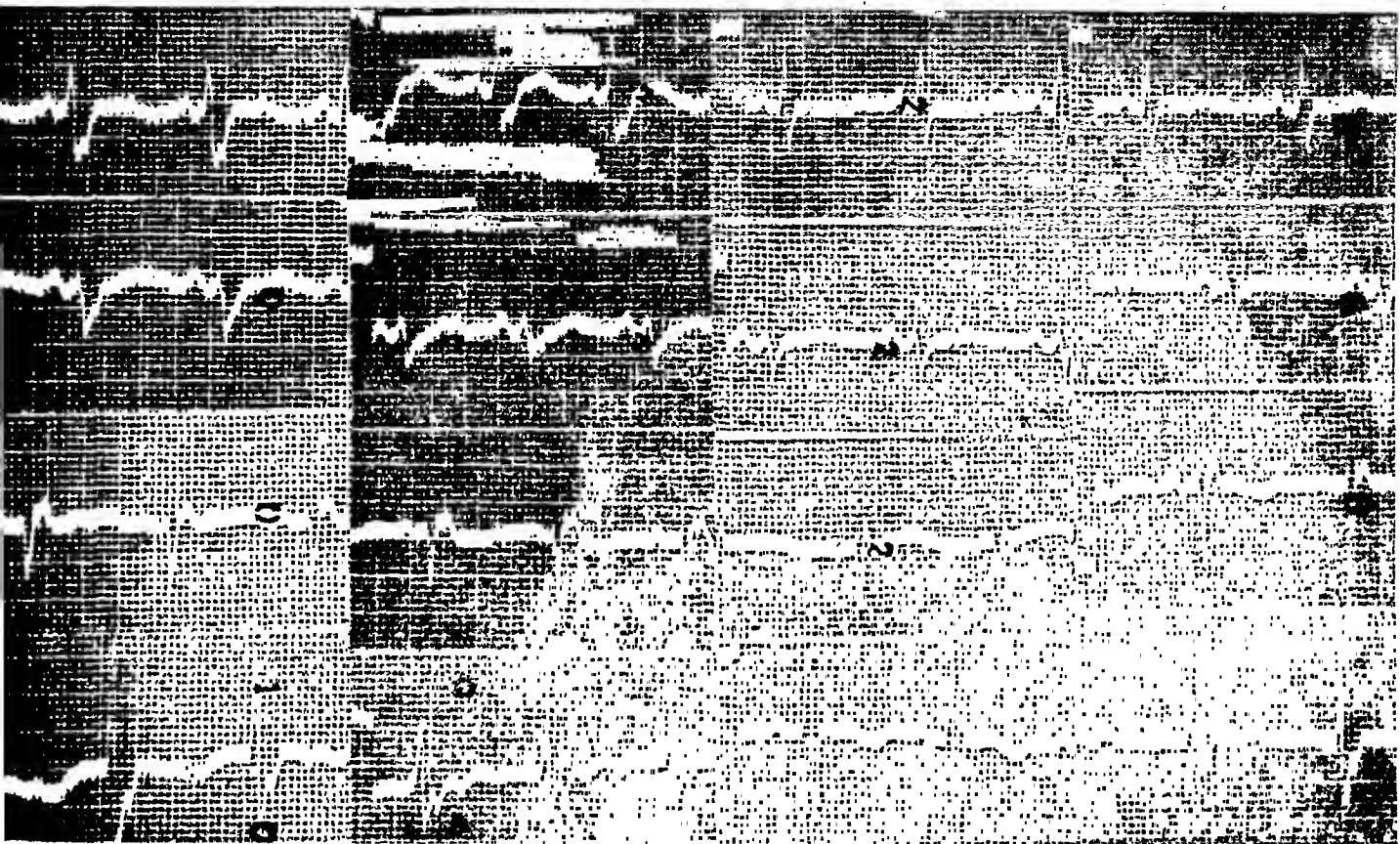


Fig. 1.—Serial electrocardiograms taken on the day of admission between syncopal seizures, on the following day, three days after admission, and seven days after, respectively. They showed normal sinus rhythm, right bundle branch block, and T-wave changes. Further records proved the diagnosis of acute myocardial infarction.

Fig. 2 shows a continuous electrocardiogram (Lead II) taken during and at the end of a typical seizure of transient ventricular fibrillation. The tracing was interrupted only twice, once in the third strip and once in the bottom strip, because the patient had a convulsion and the string could not be controlled. In the second strip the rhythm is quite regular and is similar to the tracing reported by Gertz and his co-workers⁸ as representing "ventricular flutter."

Fig. 3 shows a tracing (Lead II) during the same seizure. Strips 1 and 2 show a rapid ventricular rate which varied and oscillations which differ in shape and in amplitude. At this time the patient was extremely cyanotic and pulseless. His eyeballs rolled upward and involuntary urination occurred. The patient was apneic during this period and appeared lifeless. Strip 3 shows a slowing of the ventricular rate to 260 and sudden cessation of the attack with a short postundulatory pause and the establishment of an idioventricular rhythm. With the onset of ventricular contractions, a clonic convulsion threw the string out of the field for a few seconds. As the ventricles commenced to beat the

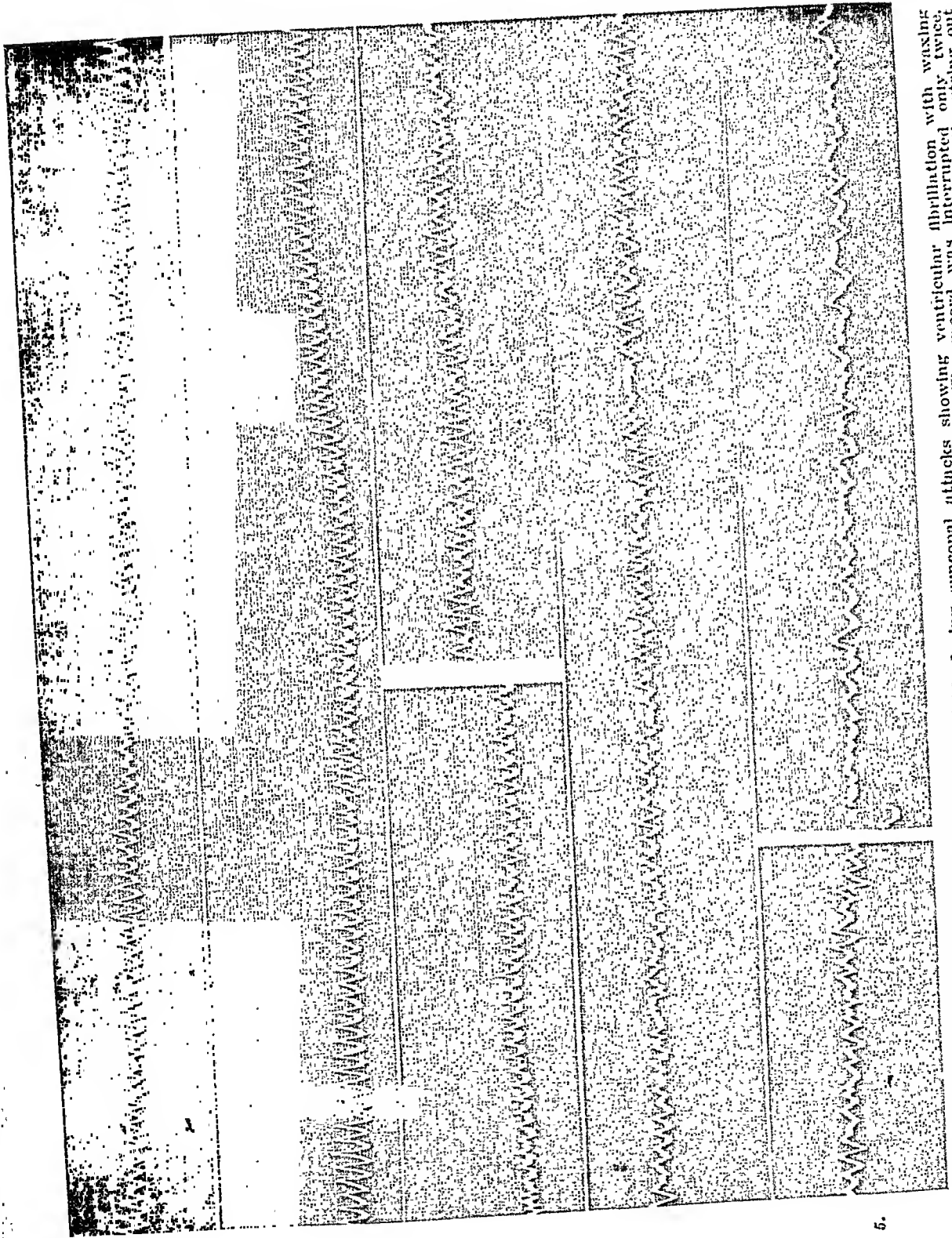


Fig. 2.—A continuous record taken on Lead II, during syncopal attacks showing ventricular fibrillation with waxing and waning of the complexes. The second strip shows a ventricular tachycardia. The record was interrupted only twice, once in the third strip and again in the bottom strip, because the patient had a clonic convulsion and threw the string out of the field.

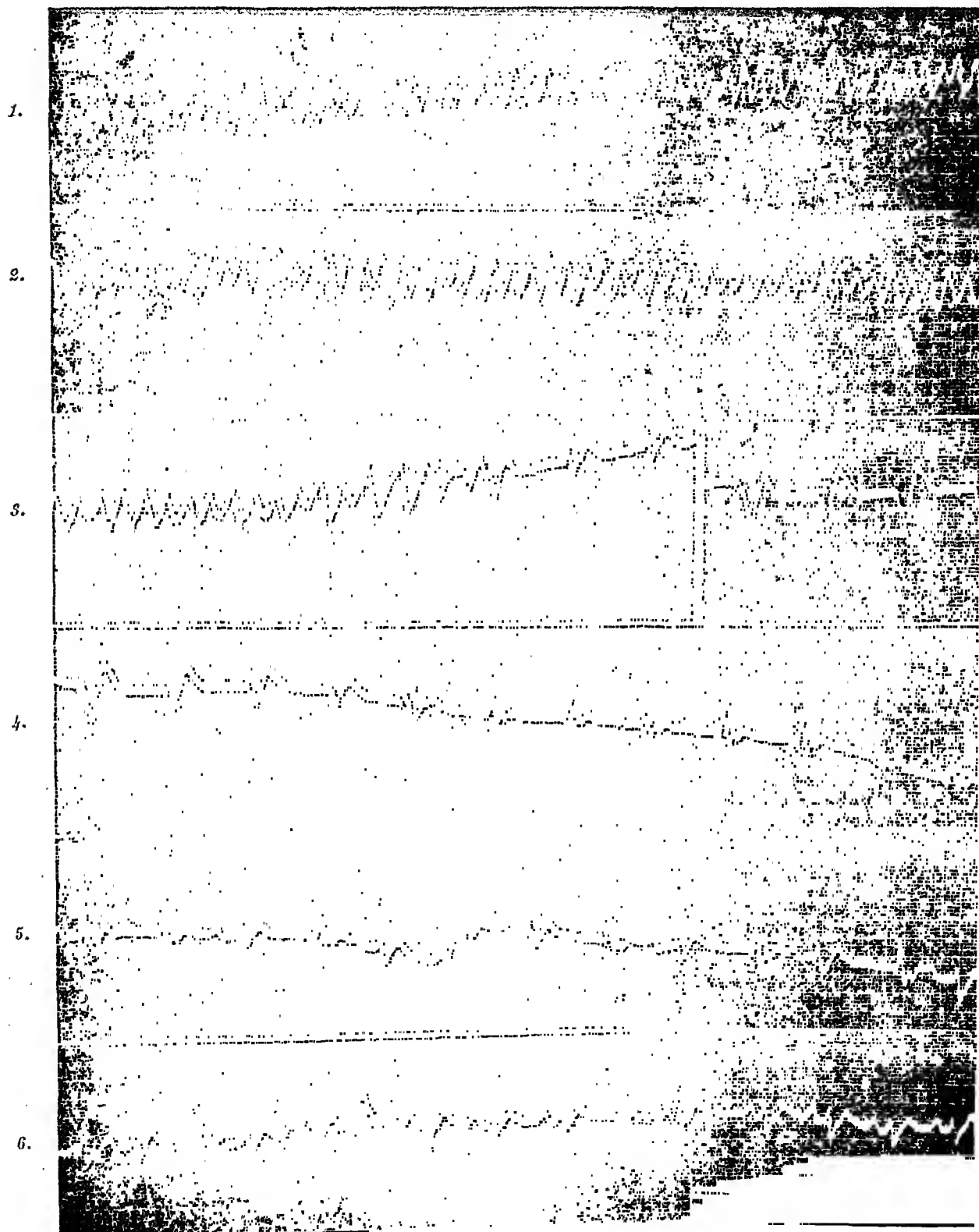


Fig. 3.—A continuous record taken on Lead II showing the end of the syncope attack. Strip 3 shows the abrupt end of the transient ventricular fibrillation followed by a post-undulatory pause and the onset of an intermediary idioventricular rhythm. In Strip 5 there appear normal complexes in which the P-R interval is increased to 0.30 second. In Strip 6, following the second ventricular ectopic beat the P-R interval is 0.24 second and at the end of the strip it is 0.20 second.

pulse became perceptible, the cyanosis cleared, and the patient appeared flushed. Gasping respirations began and as the patient regained consciousness he began to breathe regularly. Strip 4 shows idioventricular rhythm. The upright complexes occur regularly and appear to represent an idioventricular rhythm from a different focus. It is possible that these complexes may represent lower nodal rhythm with the P wave following the QRS complex. However, the notching probably is due to slurring of the QRS complex and goes to make up the QRS interval. In the next strip similar complexes appear with occasional ones which resemble the patient's "normal" complexes.

The P-R intervals of these beats are much increased, the duration being 0.30 second. The duration returns to normal in Strip 6 following two ventricular ectopic beats. The P-R interval following the second ventricular ectopic beat in Strip 6 is 0.24 second. Normal rhythm is established at the end of Strip 6.

DISCUSSION

Most of the cases reported have been associated with some form of heart block or advanced coronary arteriosclerosis. Davis and Sprague¹⁰ observe that the poor prognosis in patients with disease of the bundle tissues suggests that coordinated ventricular action is dependent upon activity of the nodal centers situated in the bundle tissue. It would seem that with complete depression of these tissues, ventricular action, save ventricular tachycardia or ventricular fibrillation, is impossible. This fact, together with the common association of heart block and ventricular fibrillation, they hold as evidence in favor of their hypothesis.

Of interest was the mode of spontaneous recovery of the heart observed in this patient. Schwartz⁴ reported two distinct modes of recovery from ventricular fibrillation. In one type, the fibrillation ceased promptly and was followed by a postundulatory pause varying from 0.8 second to 1 second. The basic ventricular rhythm did not appear for several seconds after this, and it was preceded by an idioventricular rhythm. The second type of recovery was also sudden, but was not followed by a postundulatory pause; the idioventricular rhythm arose from the last of the waves terminating the ventricular fibrillation. Fig. 3, Strip 3, shows the cessation of the ventricular fibrillation followed by a postundulatory pause and the resumption of an idioventricular rhythm.

Davis and Sprague¹⁰ discuss the mechanism of the cessation of attacks in their case. They say, "It is apparent that the depression of the bundle tissues and Purkinje system that we hold responsible for the onset of fibrillation, recovered sufficiently to permit transmission. If this recovery took place in the presence of circus movements in the ventricular muscle, these circus movements would theoretically be brought to a close by the first excitation arising from the node and distributing through the Purkinje system to the musculature. This would destroy any responsive gap and result in a general state of refractoriness from which the ventricle would recover and permit the continuity of rhythmic control from the nodal center. As long as the nodal center and Purkinje fibers

remained excitable, this rhythm would continue. With the appearance of further depression, fibrillation might be precipitated again."

Metrazol was given to this patient at first because it was thought that the syncopal attacks were due to ventricular standstill. This therapy has been suggested by Lueth.¹¹ When the nature of the disturbance was observed in the electrocardiogram, this drug was discontinued and quinidine sulfate was started by oral dosage.

Levine¹² reported the effect of quinidine in inhibiting ventricular fibrillation. Dock⁹ reported a case of recurrent attacks of syncope occurring over a period of eighteen months due presumably to ventricular fibrillation. Subsequent quinidine medication prevented these attacks. Gertz and his co-workers⁸ reported a case in which the patient had about twenty syncopal attacks. Quinidine sulfate was ineffective by mouth because of nausea and vomiting. After her last attack the patient lapsed into coma and intravenous quinidine sulfate and other measures were without avail. Davis and Sprague,¹⁰ in their paper, discuss the possible action of quinidine in initiating ventricular fibrillation.

We feel sure that the attacks which are described in this paper stopped spontaneously and not as a result of the quinidine therapy. However the quinidine sulfate was continued for several weeks. Since his discharge the patient has been followed in the Outpatient Department and has remained free of all symptoms.

SUMMARY

1. A patient with coronary artery disease and intraventricular block who suffered from fifteen seizures of unconsciousness during a period of eight hours with spontaneous recovery is reported.

2. The syncopal attacks were shown to be the result of transient ventricular fibrillation.

3. Spontaneous revival from a seizure of ventricular fibrillation was ushered in by the appearance in the electrocardiogram, of a postundulatory pause followed by idioventricular rhythm, and ventricular ectopic beats and finally by normal sinus rhythm.

REFERENCES

1. Fulton, Frank T.: Remarks Upon the Manner of Death in Coronary Thrombosis, *AM. HEART J.* 1: 138, 1925.
2. Miller, Henry: Ventricular Fibrillation as the Mechanism of Sudden Death in Patients With Coronary Occlusion, *New England J. Med.* 221: 564-569, 1939.
3. Schwartz, S. P.: Studies on Transient Ventricular Fibrillation. IV. Observations on the Clinical and Graphic Manifestations Following the Revival of the Heart From Transient Ventricular Fibrillation, *Am. J. M. Sc.* 192: 808, 1936.
4. Schwartz, S. P.: Transient Ventricular Fibrillation: A Study of the Electrocardiograms Obtained From a Patient With Auriculoventricular Dissociation and Recurrent Syncopal Attacks, *Arch. Int. Med.* 49: 282, 1932.
5. Schwartz, S. P.: Studies in Transient Ventricular Fibrillation. III. The Prefibrillatory Mechanism During Established Auriculo-Ventricular Dissociation, *Am. J. M. Sc.* 192: 153, 1936.
6. Schwartz, S. P., and Jezer, A.: Transient Ventricular Fibrillation: The Clinical and Electrocardiographic Manifestations of the Syncopal Seizures in a Patient With Auriculoventricular Dissociation, *Arch. Int. Med.* 50: 450, 1932.
7. Borg, J. F., and Johnson, C. E.: Cardiac Syncope, *AM. HEART J.* 13: 88, 1937.

8. Gertz, G., Kaplan, H. A., Kaplan, L., and Weinstein, W.: Cardiac Syncope Due to Paroxysms of Ventricular Flutter and Fibrillation, and Asystole in a Patient With Varying Degrees of A-V Block and Intraventricular Block: Report of a Case, *AM. HEART J.* 16: 225, 1938.
9. Dock, W.: Transitory Ventricular Fibrillation as a Cause of Syncope and Its Prevention by Quinidine Sulfate, *AM. HEART J.* 4: 109, 1928.
10. Davis, D., Sprague, H. B.: Ventricular Fibrillation: Its Relation to Heart Block. Report of a Case in Which Syncopal Attacks and Death Occurred in the Course of Quinidine Therapy, *AM. HEART J.* 4: 559, 1929.
11. Lueth, H. C.: The Use of Metrazol in Complete Heart Block With Adams-Stokes Syndrome, *AM. HEART J.* 16: 555, 1938.
12. Levine, H. D.: Effect of Quinidine Sulfate in Inhibiting Ventricular Fibrillation, *Arch. Int. Med.* 49: 808, 1932.

Abstracts and Reviews

Selected Abstracts

Allen, Arthur W.: Thrombosis and Embolism. Bull. New York Acad. Med. 22: 169 (April) 1946.

Considering the results of ligation of the femoral veins in 816 patients, Allen believes that thrombectomy and bilateral superficial femoral vein interruption is a safe and satisfactory method of treating early thrombophlebitis. It is a reliable method of preventing pulmonary embolism after clinical chart, signs, or symptoms, show evidence of phlebothrombosis. Prophylactic bilateral superficial femoral vein interruption is a safe and harmless procedure and prevents postoperative thrombosis and embolism. It is particularly suitable in the older age group of patients. Common femoral vein interruption is not recommended in spite of one fatal embolus, occurring in the author's series, from the profunda femoris vein after superficial femoral interruption. Serious sequelae can occur under certain circumstances from common femoral vein occlusion. The technical difficulties far outweigh any added protection to the patient. Dicoumarol in small doses appears to be safe and effective in selected patients as a preventive against thrombosis and embolism. It is useful in conjunction with femoral vein interruption after thrombosis occurs. Careful laboratory observations on the plasma prothrombin time preoperatively and after dicoumarol administration are imperative for the safety of the patient when this drug is used. NAIDE.

Samuels, S. S.: Peripheral Arterial Diseases. Post-Grad. M. J. 22: 22 (Jan.) 1946.

This is a review of some of the diagnostic and therapeutic procedures used in arteriosclerosis and thromboangiitis obliterans. The method of management of gangrene in these two diseases is described in detail. The indications and level of amputation are discussed. NAIDE.

Garber, N.: The Cure of Varicose Veins. South African M. J. 20: 67 (Feb. 9) 1946.

The local and general disturbances incident to the injection of sclerosing solutions with varicosity of the long and short saphenous veins are reviewed. The high percentage of recurrence and dangers attending ligation with retrograde instillation of sclerosing media are pointed out. The author has done 384 multiple resection operations with minor postoperative disability, no recurrence, and no mortality even in the aged. The operation lasts from one and one-half to four and one-half hours in each leg depending upon the size, number, and accessibility of the veins (presence or absence of obesity) and whether the vessels are intimately adherent to the overlying skin as a result of mild but persistent chronic cellulitis. From fifteen to thirty divisions are made under local anesthesia. The incisions lie across the course of the long saphenous and are from $\frac{1}{8}$ to $\frac{5}{16}$ inch in length. Despite the lengthy course of the operative procedure, shock is absent. Most patients are back at work within three weeks if both legs have been subjected to operation. The operation is recommended by the author as the method of choice for permanent obliteration of varicosities. NAIDE.

Gold, H., Otto, H. L., Modell, W., and Halpern, S. L.: Behavior of Synthetic Esters of Strophanthidin, the Acetate, Propionate, Butyrate, and Benzoate, in *Man. J. Pharmacol. & Exper. Therap.* 86: 301, 1946.

Patients with auricular fibrillation were studied to test the effects of the acetate, propionate, butyrate, and benzoate esters of strophanthidin. The heart rates were counted at the apex before and after the oral and intravenous administration of the drugs. All were fully effective in about thirty minutes or less when given intravenously as judged by the decline in heart rate. The oral administration of six times the effective intravenous dose of the acetate ester was not productive of a significant decline in heart rate. The benzoate was most effective by mouth in that only two and one-half times the intravenous dose was required to obtain a reduction in heart rate equivalent to that observed following its intravenous administration. Its full effect was observed in about two to three hours, and its duration of action was nearly eight hours. Orally, the propionate and butyrate esters were intermediate in their efficacy. Toxic effects were observed with all preparations and were the same as with digitalis.

FRIEDLAND.

Adlercrantz, E.: On the Neurocirculatory Syndrome (Neurocirculatory Asthenia) in Soldiers. *Acta. med. Scandinav.* 123: 219, 1946.

Sixty-eight Finnish soldiers with neurocirculatory asthenia were observed. The majority were between 20 to 29 years of age. Sixty-one were from the laboring group in contradistinction to Lewis's observation in World War I, namely that the majority of his patients left sedentary occupations to enter the army. The most frequent symptoms were previous "heart trouble," dizziness, and headache. Sweats, tremor, tachycardia, and cyanosis of the hands and feet were common. Cardiac hypertrophy as judged by x-ray examinations was present in seven patients. Only occasional patients had systolic murmurs or extrasystoles. The resting systolic pressure was 145 mm. Hg or more in 54 patients, whereas the diastolic pressure was 90 mm. Hg or less in 44 patients. Orthostatic tachycardia and hypotension were observed in 26. The electrocardiogram disclosed left ventricular preponderance in five patients and right ventricular preponderance in nine. Three patients had low or flat T waves in Leads I, II, and III which became higher or upright after exercise.

FRIEDLAND.

Teillum, G.: Pathogenetic Studies on Lupus Erythematosus Disseminatus and Related Diseases. *Acta. med. Scandinav.* 123: 126, 1946.

A pathologic study of two patients with arteriolitis granulomatosa allergica is presented and certain features common to this disease and to lupus erythematosus disseminatus, rheumatic fever, and periarteritis nodosa are pointed out. It is suggested that although the etiological agents responsible for these diseases may differ, their pathology is indicative of a common pathogenesis. A state of allergy is assumed to constitute the basis for the similarities in tissue changes, the ultimate histopathology being related to the etiological agent and the intensity and extent of tissue reaction induced by the agent.

FRIEDLAND.

Apperly, F. L., and Cary, M. K.: The Relation of Arterial Pulse Pressure to Arteriovenous Oxygen Difference, Especially in Arterial Hypertension. *Am. J. M. Sc.* 211: 467, 1946.

In a previous paper the authors showed that the arteriovenous oxygen difference in an extremity bears a reciprocal relationship to the product of the pulse pressure times the pulse rate. In this paper, the authors show that hypertensive patients as a group tend to have higher arterial pulse pressures and lower arteriovenous oxygen differences in an extremity. Assuming that the cardiac output in a hypertensive patient differs little from that of the normal individual, the data would indicate that the blood flow to an extremity is greater in the hypertensive patient than in the normal, and that there is, therefore, a greater proportion of blood flow to muscular areas than to the viscera in hypertensive patients.

FRIEDLAND.

Straus, R., Dominguez, R., and Merliss, R.: Slowly Progressive Oclusive Thrombosis of the Abdominal Portion of the Aorta. *Am. J. M. Sc.* 211: 421 (April) 1946.

Three cases of slowly progressive oclusive thrombosis of the abdominal portion of the aorta are presented. The disease is usually secondary to a severe uleerative arterio-sclerosis of the arterial wall, but may follow an embolism to the bifureation of the aorta, or more rarely, thrombosis of the pelvie arteries after irradiation. Its mean autopsy incidence is 0.12 per cent. The characteristics of this syndrome that permit differentiation from other forms of aortie oclusion are: insidious onset; protracted course; usually, but not always, absence of gangrene; absence of pulses in both lower extremities; intermittent claudication; and the appearance of arterial hypertension or of signs of viscerai infarection years after the onset of elaudication in the legs.

NAIDE.

Ranström, S.: Amyloidosis Myocardii. *Aeta. med. Scandinav.* 123: 111 (No. 2) 1946.

Three cases of "primary" cardia amyloidosis are reported and the thirty cases in the literature are reviewed. The only fairly constant clinical findings were rapid sedimentation rates, thought to be the result of hyperglobulinemia; and a slight or moderate hypotension. Low voltage in the electrocardiogram and signs of myocardial insufficiency sometimes occurred. The heart was frequently enlarged, but its gross appearance in one of the author's cases was normal except for hypertrophy. Usually there was a greenish yellow coloration and a semiopaque sheen when involvement of the myocardium was severe and diffuse. Microscopically there might be diffuse or spotty interstitial deposits, though amyloid was never found actually within the muscle fibers themselves. Subepicardial, subendocardial, and valvular deposition was sometimes seen, the mitral valve was involved in one of the author's cases. Another type of deposition was amyloidosis of the smaller coronary artery branches, in which the media and intima were almost entirely replaced by amyloid and surrounded by a relatively normal adventitia. No definite cause for the amyloid was found in any of the three cases reported by the author.

SAYEN.

Gladnikoff, H.: The Roentgenological Picture of the Coarctation of the Aorta and Its Anatomical Basis. *Aeta. radiol.* 27: 8 (No. 1) 1946.

The author correlates the roentgenologic picture with the operative findings in three cases of coarctation of the aorta which were repaired by Crafoord. He emphasizes that the leftward convexity in the upper mediastinum was the dilated left subclavian artery although it had sometimes been mistaken for the aortic knob. In all three cases the coarcted area lay at the angle of juncture of the subclavian artery and the aortic arch or 3 to 5 cm. below it, but was drawn within the mediastinal shadow. Below the depression in the left mediastinal border the thoracic aorta could be seen, although not clearly. The aortic knob in the anteroposterior and the arch in the left anterior oblique views were poorly seen in spite of hypertension which was expected to increase visibility. This was explained by the shortening effects of low pressure in the aorta below the coarctation, by contraction of the adjacent aortic wall, and by the fact that the aorta was pulled inward, downward, and posteriorly by the shortening of the ductus botalli. The poor roentgenologic visualization is believed to be due to the effect of coarctation on aortic length and position. Hence, the disappearance of the shadow of the aortic arch in the x-ray is by no means pathognomic of coarctation and can occur in any condition that causes shortening of the aorta, such as congenital hypoplasia.

SAYEN.

Savilahti, M.: On the Normal and Pathological P-Q Time of the Electrocardiogram. *Aeta. med. Scandinav.* 123: 252 (No. 3) 1946.

From statistics based on 872 cases of all ages the author concludes that the length of the P-Q interval is not directly related to the heart rate and that it remains very constant in any particular healthy individual except for a gradual increase with age in childhood.

and adolescence. The upper limits of normal for the younger age groups in the series were 0.15 second below the age of 5 years, 0.17 second between 5 and 10 years, and 0.20 second after the age of 15 years. In fever, the standing posture, and after exercise, the P-Q interval often shortened; but this was not proportionate to the increased heart rate in such states and not infrequently occurred when the rate remained relatively constant.

SAYEN.

Bang, J.: A Peculiar Conduction Disturbance Persisting Latently After Recovery From Complete Heart Block and Disclosed Only by Electrocardiography Following Exercise. *Acta. med. Scandinav.* 123: 551 (No. 6) 1946.

The author reports the case of a 15-year-old boy who developed complete heart block three weeks after a streptococcal tonsillitis and was subject to attacks of syncope associated with complete pallor and mild spasms. The heart rate during block was 40 per minute; the blood pressure was 90/80, and the sedimentation rate was 56 mm. per hour. Leucocytosis was present and antistreptolysin titers were significantly elevated. Recovery was gradual; a two-to-one heart block was present on the seventh day, and partial block was recorded on the ninth day after onset. The P-R interval was markedly prolonged for thirteen days, and on discharge from the hospital it was still as high as 0.22 second.

The patient was re-examined one year later and the abnormal P-R interval, which was still present, was the only significant finding. After violent exercise, a marked arrhythmia occurred, consisting of short runs of six or seven rapid beats, and a steadily increasing P-R interval which reached 0.30 second, after which there was a slight pause, which may have represented a dropped beat, and the rate decreased sharply. The next several beats were at a slow tempo with a P-R interval of 0.17 second. This cycle was repeated several times, and, after a lasso of about twenty minutes, although the rate was regular, the P-R interval was noted to be 0.30 second, diminishing only gradually to 0.23 second. Re-examination the following year showed the identical picture, although the patient felt quite well and led an active life throughout the period of examination and the intervals between.

SAYEN.

Magnasson, P.: Auricular Standstill. *Acta med. Scandinav.* 123: 519 (No. 6) 1946.

Three new cases are added to the thirty-one collected from the literature. The criteria were a regular ventricular rate and no auricular deflections in any limb or precordial lead. The commonest causes of the disorder appeared to be digitalis or quinidine toxicity. The authors emphasize the necessity of frequent electrocardiograms in patients who are receiving large doses of digitalis with normal rhythm or patients with auricular fibrillation who regain normal rhythm, since there are no diagnostic clinical symptoms of auricular standstill and since in animals this condition is frequently a precursor of ventricular standstill.

SAYEN.

Lindqvist, T., and Söderström, N.: An Unusual Electrocardiographic Manifestation of Intra-Auricular Dissociation in a Pair of Identical Twins. *Acta med. Scandinav.* 123: (No. 1) 1946.

Electrocardiographic studies were made in a pair of 42-year-old identical twins with absolute arrhythmias. They were found to have a totally irregular ventricular rate but with P waves preceding all complexes. The P-R intervals varied from 0.23 to 0.5 second. Rare periods of complete atrioventricular dissociation occurred. Most of the P waves in limb leads were double, the two peaks separated by 0.08 to 0.1 second. The second (usually inverted) component of these P waves was simultaneous with the intrinsic auricular deflection in esophageal leads, while the first component was largest in a precordial lead near the sternum in the third right intercostal space. They were thought to be, respectively, left and right auricular in origin and their separateness was attributed to delayed inter-

auricular conduction. With increased heart rates small irregular *f* waves appeared in one case, in addition to the double P waves. Administration of $\frac{1}{2}$ mg. of atropine sulfate caused the base line to show coarse flutterlike waves, every other one being accompanied by a P wave. The authors believe that the bizarre mechanism was caused by a localized area of constant fibrillation, probably in the right auricle, surrounded by a ring of refractory muscle transmitting a limited number of impulses to which the remaining muscle of the right and left auricles responded usually, and the ventricles always, with a totally irregular rhythm.

SAYEN.

Lequieme, J., and Denolin, H.: Circulatory Changes Following the Injection of Hypertonic Saline Solutions. Application to the Study of Angina Pectoris. *Arch. d. mal. du cœur*. 38: 231 (Sept.-Oct.) 1945.

Observations were made on the effect of intravenous injections of hypertonic saline solution in patients who had coronary disease. Forty patients were studied, all of whom presented a typical history of angina of effort. The technique involved recording the electrocardiogram from the limb leads before, immediately after, and five minutes after the rapid intravenous injection of 40 c.c. of 20 per cent saline solution.

The procedure was well tolerated. All patients noted a sensation of warmth resulting from the injection. Six patients had anginal pain and, in two instances, the pain was severe. In 38 of the 40 patients, the heart rate was accelerated. In 14 patients, the electrocardiogram showed transient S-T interval deviation which was most conspicuous in Leads II and III. In 12 patients, the T waves became flattened in Leads I and II. In 14 patients, the injection produced no significant change in the electrocardiogram. It is noteworthy that in the latter group, most of the patients had abnormal electrocardiograms before the test.

In normal subjects and in cardiac patients without coronary disease, the injection produced tachycardia and occasionally some flattening of the T waves, but there have been no instances of S-T interval deviation. The effect of intravenous hypertonic saline on the electrocardiogram of patients who have coronary disease is attributed to the resultant increase in work of the heart. The procedure is recommended as a substitute for the exercise test in the diagnosis of angina pectoris.

LAPLACE.

Gillman, T., and Gillman, J.: The Value of Speransky's Method of Spinal Pumping in the Treatment of Rheumatic Fever and Rheumatoid Arthritis. *Am. J. M. Sc.* 211: 448 (April) 1946.

The method of spinal pumping first described by Speransky, in 1935, was utilized by these authors in the treatment of 70 patients suffering from acute, subacute, or chronic forms of rheumatism with joint involvement. All the patients, with three exceptions, were adults. In all but two instances, 10 Gm. of sodium salicylate in divided doses were administered orally or rectally twenty-four hours before pumping and for twenty-four to forty-eight hours after pumping. The actual "pumping" consists of withdrawal into the barrel of a 10 c.c. syringe of cerebrospinal fluid, and then re-introducing the fluid into the subdural space. This procedure is performed with the patient in the left or right lateral position. In most of the cases in this series, 10 c.c. of cerebrospinal fluid (only 6 c.c. in children) were withdrawn and re-introduced twenty times. At the completion of the spinal pumping, 10 c.c. of the spinal fluid were removed and discarded. This procedure usually takes forty or fifty minutes.

Of 48 cases of acute or subacute arthritis, 42 showed objective evidence of improvement. The majority of the patients (70 per cent) were relieved within twelve to thirty-six hours, and another 20 per cent responded at the end of seventy-two hours. The remaining cases showed a steady improvement which was maximum at the end of two to three weeks. No recoveries among chronic cases were observed but 12 of the 22 cases were considerably relieved.

In general, the results obtained confirm those recorded by Speransky. It is the opinion of the authors, in agreement with Speransky and others, that the nervous system plays a considerable role in the pathogenesis of rheumatic fever, rheumatoid arthritis, and other inflammatory processes, and that spinal pumping produces some interference with the nervous mechanism which leads to favorable responses in the various forms of rheumatism resistant to the usual forms of therapy.

BELLET.

Kittredge, W. E., and Brown, H. G.: The Present Status of Unilateral Renal Hypertension. *J. Urol.* 55: 213 (March) 1946.

The present status of unilateral kidney pathology in producing hypertension is considered, with particular reference to the indications for nephrectomy of the diseased kidney. This procedure has been performed in every type of surgical kidney in recent years with the hope of relieving hypertension.

Numerous clinical investigators have pointed out that the influence of hypertension in a series of patients with unilateral kidney disease is actually no greater than the incidence in any group of patients of comparable age chosen at random. From a study of conflicting observations and careful follow-up of patients, the authors have reached the following conclusions: no permanent change in blood pressure can be reasonably expected to follow removal of a functionless kidney, whether the diseased kidney was the original cause of the hypertension or not; the renal lesion associated with hypertension which was most amenable to surgical treatment was atrophic pyelonephritis; and the next most common lesion associated with hypertension was renal neoplasm, followed by renal lithiasis, hydronephrosis, tuberculosis, and polycystic kidneys.

Although hypertension associated with surgical lesions was often relieved by nephrectomy, the blood pressure often also returns to normal following nephrolithotomy and renal drainage. This reduction in blood pressure may persist for a year or more after operation and then return to its previous level. This may be explained on the grounds that a toxic or irritant lesion has been eliminated and that, when this influence has worn off, the underlying essential hypertension reasserts itself.

BELLET.

Mokotoff, R., Brams, W., Katz, L. N., and Howell, K. M.: The Treatment of Bacterial Endocarditis With Penicillin, Results of 17 Consecutive Unselected Cases. *Am. J. M. Sc.* 211: 395 (April) 1946.

These authors report a series of 17 consecutive patients with subacute bacterial endocarditis, 14 of whom have fully recovered from their infection. These patients were observed for a period of eight to twenty months following cessation of therapy. The susceptibility of the organism to penicillin is one of the most important factors in determining the outcome of therapy. These authors agree with Loewe that the best results are obtained when penicillin blood serum levels are maintained between five and ten times the "in vitro" sensitivity figure. Since investigation has shown that there is little penicillin remaining in the blood serum sixty to seventy-five minutes after a single intramuscular injection and practically none at the end of two hours, intermittent intramuscular injections were employed every hour on the hour day and night for the entire period of treatment. The usual daily dose was 200,000 to 300,000 units; the more resistant cases received 1 million to 3 million units. The usual course was planned for twenty-one days. It is of some interest that one of their patients, who died because of progressively severe congestive failure (six months after successful penicillin therapy) revealed at autopsy healed subacute bacterial endocarditis of the mitral and aortic valves.

BELLET.

Heuper, W. O.: Atheromatosis in Dogs Following Repeated Intravenous Injections of Hydroxycellulose. *Arch. Path.* 41: 130 (Feb.) 1946.

Heuper, continuing his studies on the genesis of atheromatosis, recorded the effects of intravenous injections of hydroxycellulose in various concentrations. This was injected daily for periods of six to twelve weeks. The viscosity of the solutions was an important

factor in the production of atheromatosis; the least viscid solution was responsible for the most severe and generalized lesions. Typical foam cells, fibrous cushions, and circumscribed hyaline thickenings of the intima, often associated with degeneration and calcification of the media of the aorta and of the medium-sized branches were noted in the dogs receiving injections of hydroxycellulose of medium and low viscosity. Solutions of heavy viscosity produced no intravascular pathologic changes. On the other hand, the latter injections resulted in leucopenia and anemia.

GOULEY.

Koletsky, S.: Gross Vascularity of the Mitral Valve as a Stigma of Rheumatic Heart Disease. Am. J. Path. 22: 351 (March) 1946.

Koletsky studied the vascularity of the mitral valve of 150 hearts with and without gross rheumatic heart disease, all of which showed gross vascularity of the anterior mitral leaflet. The hearts observed were divided into three groups as follows: Group 1 contained 50 hearts with no conclusive gross rheumatic disease, Group 2 included 50 hearts with non-deforming rheumatic mitral disease, and Group 3 included the 50 hearts with mitral stenosis. Fifty nonrheumatic adult hearts with grossly avascular mitral valves were included as a control. It was found that a large percentage of hearts with no gross rheumatic disease which presented gross vascularization of the mitral valve leaflet showed microscopically endocardial reduplications and cellular exudate characteristic of rheumatic valvulitis. Group 2 has the same microscopic stigmata but in a higher percentage. The group of hearts with mitral stenosis showed the highest percentage. The control group showed very little or no vascularity of the anterior mitral leaflet and no microscopic stigmata.

Koletsky concludes that hearts with diffuse gross vascularity of the mitral valve almost uniformly show microscopic stigmata of inflammatory disease of rheumatic origin. The presence of small thick-walled arteries of musculoelastic type in the mitral valve is considered by Koletsky to be characteristic and probably pathognomic of rheumatic fever.

GOULEY.

Askey, J. M.: Quinidine in the Treatment of Auricular Fibrillation in Association With Congestive Failure. Ann. Int. Med. 24: 371 (March) 1946.

Quinidine is ordinarily considered to be contraindicated for auricular fibrillation in association with congestive failure, or in association with severe heart disease. In certain instances, however, its use has been lifesaving and in a number of desperately sick patients, it has improved the patient's cardiac status for many months. The real dangers of quinidine are those of embolism, sudden death, and production of ectopic ventricular rhythms. This study concerns itself with a statistical evaluation of the dangers of quinidine, particularly in the presence of congestive heart failure and serious heart disease. This is done in an attempt to determine any deleterious effects in such patients which would outweigh any beneficial action which may be desired. This author found that quinidine is apparently no more dangerous to patients with congestive failure than the natural dangers of the heart condition itself. Among patients with congestive failure who improve adequately with digitalis and rest, along with other measures, quinidine therapy might be tried. The presence of conduction defects appears to be a contraindication to its use. In the absence of such abnormalities there would seem to be no reason why every patient with uncontrolled congestive failure should not be given a chance with quinidine. Even if the ventricular rate is slow, reversion to sinus rhythm may relieve congestive failure. The usually accepted contraindications in the use of quinidine, namely congestive failure, repeated embolism, long standing auricular fibrillation, and conduction defects, are not considered to be absolute contraindications.

BELLET.

Fox, M. J., and Bortin, M. M.: Rubella in Pregnancy Causing Malformations in Newborn. J. A. M. A. 130: 568 (March 2) 1946.

Much interest has recently developed concerning the influence of rubella early in pregnancy upon the production of congenital malformations. Some authors have even suggested therapeutic abortion be performed when rubella occurs early in pregnancy. In a

series of eleven cases observed by these authors, only one evidenced a pathologic course. Their records do not justify the conclusions of previous authors concerning the influence of rubella in producing congenital malformation. They suggest that this subject deserves further careful consideration and investigation.

BELLEF.

Epidemiology Unit No. 82, U. S. Naval Hospital, Treasure Island: Observations on the Treatment of Scarlet Fever With Penicillin. *Am. J. M. Sc.* 211: 417 (April) 1946.

In view of recent reports showing the efficacy of penicillin therapy in the treatment of streptococcal pharyngitis and scarlet fever, an investigation was made on 118 patients who were members of the Naval personnel. All patients treated with penicillin showed a good clinical response in that the temperature dropped to normal and there was marked symptomatic improvement in twenty-four to forty-eight hours. The incidence of complications was found to be highest (31 per cent) in that group receiving 240,000 units in six days and lowest (6 per cent) in the group receiving 480,000 units in eight days.

The rate of recurrence of positive cultures was also lowest (8 per cent) in the group receiving the higher penicillin dosage. It was therefore concluded that the use of penicillin over an eight-day period is a satisfactory method for the treatment of scarlet fever and for preventing the establishment of a beta hemolytic streptococcus carrier state in the convalescent patients.

BELLEF.

Hubacker, V. O.: Beitrag zur Beurteilung des runden Überganges von R und die ST Strecke in Elektrokardiogramm. *Helvet. med. acta*, Series A (March) 1946.

1. The hypothesis according to which the rounded transition of the R wave to the S-T interval is of cardiac origin must be definitely abandoned.

2. The rounded transitions occur when polarization is small within the electric circuit patient-electrocardiograph; they disappear and become pointed S waves when polarization within this circuit is considerable.

3. The polarization capacity of the skin is small in the presence of poor blood flow and large when the flow is good.

4. The signs of polarization in the electrocardiogram depend upon the form of the latter (the part above and below the isoelectric line), upon the apparatus (resistance), and upon the functional processes in the skin of the patient (blood flow).

AUTHOR.

Davidson, C. S., Lewis, J. H., Tagnon, H. J., Adams, M. A., and Taylor, F. H. L.: Medical Shock: Abnormal Biochemical Changes in Patients With Severe, Acute Medical Illnesses, With and Without Peripheral Vascular Failure. *New England J. Med.* 234: 279 (Feb. 28) 1946.

This study was undertaken to determine the relationship of peripheral vascular failure, uncomplicated by traumatic conditions, to the biochemical changes which accompany shock in experimental animals and injury in man. Observations were made on a series of twelve patients who were suffering from severe medical illness with or without the presence of peripheral vascular failure. The presence of diabetes mellitus was excluded.

It was found that the biochemical abnormalities which occurred in these patients were similar to those which occur in various traumatic conditions, hemorrhage, and anoxia. They consisted of hyperglycemia, lactic acidemia, a fall in the bicarbonate reserve, reduction in oxygen saturation of the peripheral blood, frequent elevation of the alpha amino nitrogen of the blood plasma, and usually a lengthening of the prothrombin time and an elevation of the icterus index. Although the primordial cause is not known, the authors suggest the possibility that tissue anoxia which accompanies peripheral vascular failure, leads to increase in glycogenolysis and possible gluconeogenesis with resultant hyperglycemia. A marked correlation was found between the profoundness of the biochemical abnormality and the degree of the vascular failure.

LAPLACE.

Announcements

INTER-AMERICAN CONGRESS OF CARDIOLOGY, MEXICO CITY, OCT. 6-12, 1946

There will be an Inter-American Congress of Cardiology in Mexico City, Oct. 6-12, 1946. The meetings will be held in the Institute of Cardiology. This Congress is being sponsored by the Inter-American Society of Cardiology and the National Societies of Cardiology of the Continent. Prominent European cardiologists have been invited to attend. The American Heart Association has been designated as the representative of this Congress in the United States, and all applications to participate in the scientific meetings or to attend as guests should be addressed to this Association, 1790 Broadway, New York 19, New York.

FELLOWSHIPS AVAILABLE FOR THE STUDY OF RHEUMATIC FEVER

The American Council on Rheumatic Fever of the American Heart Association announces that it will entertain applications for American Legion fellowships for the study of rheumatic fever. Applications will be accepted from recognized institutions concerned with the study of rheumatic fever and rheumatic heart disease. Two fellowships are available. Each is for a period of three years and carries a stipend of \$3,500, \$4,000, and \$5,000 for the first, second, and third years, respectively.

Each application should supply information concerning the institution, the projected study, and the individual proposed for the fellowship. Applications will be received until Aug. 1, 1946, and will become effective Sept. 1, 1946.

The American Legion fellowships for the study of rheumatic fever have been made available by a grant from the American Legion and the Women's Auxiliary of the American Legion as part of their program of fostering research in rheumatic fever and rheumatic heart disease through the American Council on Rheumatic Fever of the American Heart Association.

Errata

Mainly because of distance and the difficulty of rapid mail communication, there were several errors in the paper by Dr. R. H. Goetz of Cape Town, South Africa, on "The Rate and Control of the Blood Flow Through the Skin of the Lower Extremities," which appeared in the February, 1946, issue of the JOURNAL, Volume 31. We regret exceedingly that these errors were made. We are glad to publish the following corrections so that the author's intended meaning will be clear.

1. Page 154, the second line of the last paragraph should read "multiple pinpricks" and not "multiple principles."

2. Page 164, five lines from the top of the page, should read: "Fig. 14 shows one of the arteries of the digit tested" and not "Fig. 14 shows the results of testing one of the arteries of the digit."

3. Page 172, the sixth line of the second paragraph should read: "This decrease in blood flow following body heating has been explained as follows: Since body heating causes a release of the vasomotor tone in the normally innervated extremities, it follows . . . to the unsympathectomized one."

4. Page 177, the last sentence in the first paragraph under Discussion should read: "Failure of the pulse has *therefore* to be accounted for" not "Failure . . . has *yet* to be . . ."

5. Page 177, the first line of the last paragraph should read: "The possibility of such a wide range in blood flow, under the control of the autonomic nervous system, is part of the body's mechanism for temperature regulation." Not "The possibility exists . . ."

American Heart Association, Inc.

1790 BROADWAY AT 58TH STREET, NEW YORK, N. Y.

DR. ROY W. SCOTT
President

DR. HOWARD F. WEST
Vice-President

DR. GEORGE R. HERMANN
Treasurer

DR. HOWARD B. SPRAGUE
Secretary

BOARD OF DIRECTORS

*DR. EDGAR V. ALLEN Rochester, Minn.
DR. ARLIE R. BARNES Rochester, Minn.
DR. WILLIAM H. BUNN Youngstown, Ohio
DR. CLARENCE de la CHAPELLE New York City
DR. NORMAN E. FREEMAN Philadelphia
*DR. TINSLEY R. HARRISON Dallas
DR. GEORGE R. HERMANN Galveston
DR. T. DUCKETT JONES Boston
DR. LOUIS N. KATZ Chicago
*DR. SAMUEL A. LEVINE Boston
DR. GILBERT MARQUARDT Chicago
*DR. H. M. MARVIN New Haven
*DR. EDWIN P. MAYNARD, Jr. Brooklyn
*DR. THOMAS M. McMILLAN Philadelphia
DR. JONATHAN MEAKINS Montreal
DR. E. STERLING NICHOL Miami

DR. HAROLD E. B. PARDEE New York City
DR. WILLIAM B. PORTER Richmond, Va.
DR. DAVID D. RUTSTEIN New York City
*DR. JOHN J. SAMPSON San Francisco
*DR. ROY W. SCOTT Cleveland
DR. FRED M. SMITH Iowa City
DR. HOWARD B. SPRAGUE Boston
DR. GEORGE F. STRONG Vancouver, B.C., Can.
DR. WILLIAM D. STROUD Philadelphia
DR. HOMER F. SWIFT New York City
DR. WILLIAM P. THOMPSON Los Angeles
DR. HARRY E. UNGERLEIDER New York City
*DR. HOWARD F. WEST Los Angeles
DR. PAUL D. WHITE Boston
DR. FRANK N. WILSON Ann Arbor
*DR. IRVING S. WRIGHT New York City
DR. WALLACE M. YATER Washington, D. C.

*EXECUTIVE COMMITTEE

DR. H. M. MARVIN, *Acting Executive Secretary*

ANNA S. WRIGHT, *Office Secretary*

TELEPHONE, CIRCLE 5-8000

THE American Heart Association is the only national organization devoted to educational work relating to diseases of the heart. Its activities are under the control and guidance of a Board of Directors composed of thirty-three eminent physicians who represent every portion of the country.

A central office is maintained for the coordination and distribution of important information. From it there issues a steady stream of books, pamphlets, charts, films, lantern slides, and similar educational material concerned with the recognition, prevention, or treatment of diseases of the heart, which are now the leading cause of death in the United States. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning the circulation of blood and lymph. Any physician or investigator may become a member of the section after election to the American Heart Association and payment of dues to that organization.

The income from membership and donations provides the sole financial support of the Association. Lack of adequate funds seriously hampers more intensive educational activity and the support of important investigative work.

Annual membership is \$5.00. Journal membership at \$11.00 includes a year's subscription to the AMERICAN HEART JOURNAL (January-December) and annual membership in the Association. The Journal alone is \$10.00 per year.

The Association earnestly solicits your support and suggestions for its work. Membership application blanks will be sent on request. Donations will be gratefully received and promptly acknowledged.

American Heart Journal

VOL. 32

AUGUST, 1946

No. 2

Original Communications

THE PRECORDIAL ELECTROCARDIOGRAM IN HIGH LATERAL MYOCARDIAL INFARCTION

FRANCIS F. ROSENBAUM, M.D., FRANK N. WILSON, M.D., AND
FRANKLIN D. JOHNSTON, M.D.
ANN ARBOR, MICH.

THE observations upon which this report is based were made on a group of six patients whose routine standard and unipolar extremity electrocardiograms showed changes suggestive of myocardial infarction. The usual precordial leads presented no more and often much less evidence pointing to this diagnosis. On the other hand, extensive exploration of the left anterolateral, lateral, and posterolateral aspects of the thorax at levels higher than those usually studied yielded more significant electrocardiographic data.

Four of the six patients gave a definite history of a coronary accident a few days to one year prior to the time of our observations; one of them has recently developed a posterior lesion one year after an earlier high posterolateral lesion. In two cases the history was merely suggestive of infarction; one patient had angina pectoris, intermittent claudication, and an old posterior infarct, and the other had moderate congestive failure alone.

In four patients the changes most characteristic of myocardial infarction were recorded in the vertical line of Lead V_3 , Lead V_4 , or Lead V_5 but one to three intercostal spaces above the level from which these leads are taken. In these cases a diagnosis of high anterolateral infarction was made. In one patient, the most striking changes occurred in leads from the anterior and midaxillary lines at levels two or three intercostal spaces higher than the usual Lead V_5 or V_6 ; in this instance, the diagnosis was high lateral infarction. In one case the most definite changes were seen in records from points high in the left posterior axillary and the left scapular lines and were attributed to a high posterolateral

From the Department of Internal Medicine, University of Michigan Medical School. Much of the work upon which this article is based was done under a grant from the Horace H. Rackham School of Graduate Studies.

Presented in part before the Eighteenth Annual Meeting of the Central Society for Clinical Research, Chicago, Nov. 3, 1945.

Received for publication Feb. 8, 1946.

infarct. The observations made were not identical in all patients since only as the study progressed were the most advantageous points for exploration revealed.*

CLINICAL OBSERVATIONS

High Anterolateral Infarction.—The first four cases to be discussed are considered examples of high anterolateral infarction.

CASE 1.—H. K., a 41-year-old bus driver entered the University Hospital on June 23, 1944, for treatment of a left hemiplegia which had appeared suddenly one year earlier. For two weeks prior to the occurrence of the paralysis he had experienced frequent attacks of pain in the chest while driving his bus. The attacks were severe enough to make him stop to rest and he was finally forced to stop working because of them. In May, 1943, while sitting in a restaurant, he suddenly developed a left hemiplegia. He was under treatment in a hospital for one month; his blood pressure was said to have been high during that period. He was able to walk with difficulty by August, 1943, but there had been little change in his condition for ten months. There was a strong familial history of cardiovascular disorders.

Examination showed a left spastic hemiplegia with a left facial paresis of central type. The retinal vessels exhibited minimal arteriosclerosis. The heart sounds were normal. The blood pressure was 120/80. There were occasional extrasystoles. The usual laboratory tests, including the blood Kahn reaction, were negative. Roentgenographic examination of the thorax showed slight cardiac enlargement and slight pulmonary congestion.

Electrocardiographic studies were made on July 28, 29, and 30. Only those made on the last day, when supplementary precordial leads were taken, are reproduced (Fig. 1). The standard and unipolar limb leads exhibit slight left axis deviation with small Q waves and slight terminal inversion of the T waves in Leads I and V_L . The usual precordial leads show tiny Q waves in Leads V_2 , V_3 , and V_4 and terminal inversion of the T waves in Leads V_3 , V_4 , and V_5 . In the case of normal subjects there is a rapid increase in the size of the R waves as the exploring electrode is moved toward the left side of the precordium. In this case, therefore, the R waves are unexpectedly small in Leads V_3 , V_4 , and V_5 . It should also be noted that R is taller in Lead V_6 than it is in Lead V_5 ; the opposite is normal.¹

The tracings from points in the left midclavicular line (vertical line of Lead V_4) at higher levels (third and fourth intercostal spaces) show both QRS and T-wave changes which are strongly suggestive, if not diagnostic, of myocardial infarction. Similar but less striking alterations occur in the leads from points at the same horizontal levels but in the left anterior axillary line (line of Lead V_5). Only very slight inversion of the T waves is seen in the record from a point in the midaxillary line (line of Lead V_5) and at the level of the third intercostal space.

CASE 2.—C. K., a 40-year-old engineer entered the Heart Station of the University Hospital on March 3, 1944. Two months previously he developed burning substernal pain which

*After the first few cases had been studied, we adopted the plan of taking supplementary unipolar leads from points at the intersections of lines on the horizontal level of the fourth, third, or second intercostal space at the left sternal margin and the vertical lines of Lead V_3 , Lead V_4 (left midclavicular line), Lead V_5 (left anterior axillary line), Lead V_6 (left midaxillary line), Lead V_7 (left posterior axillary line), etc., as indicated.

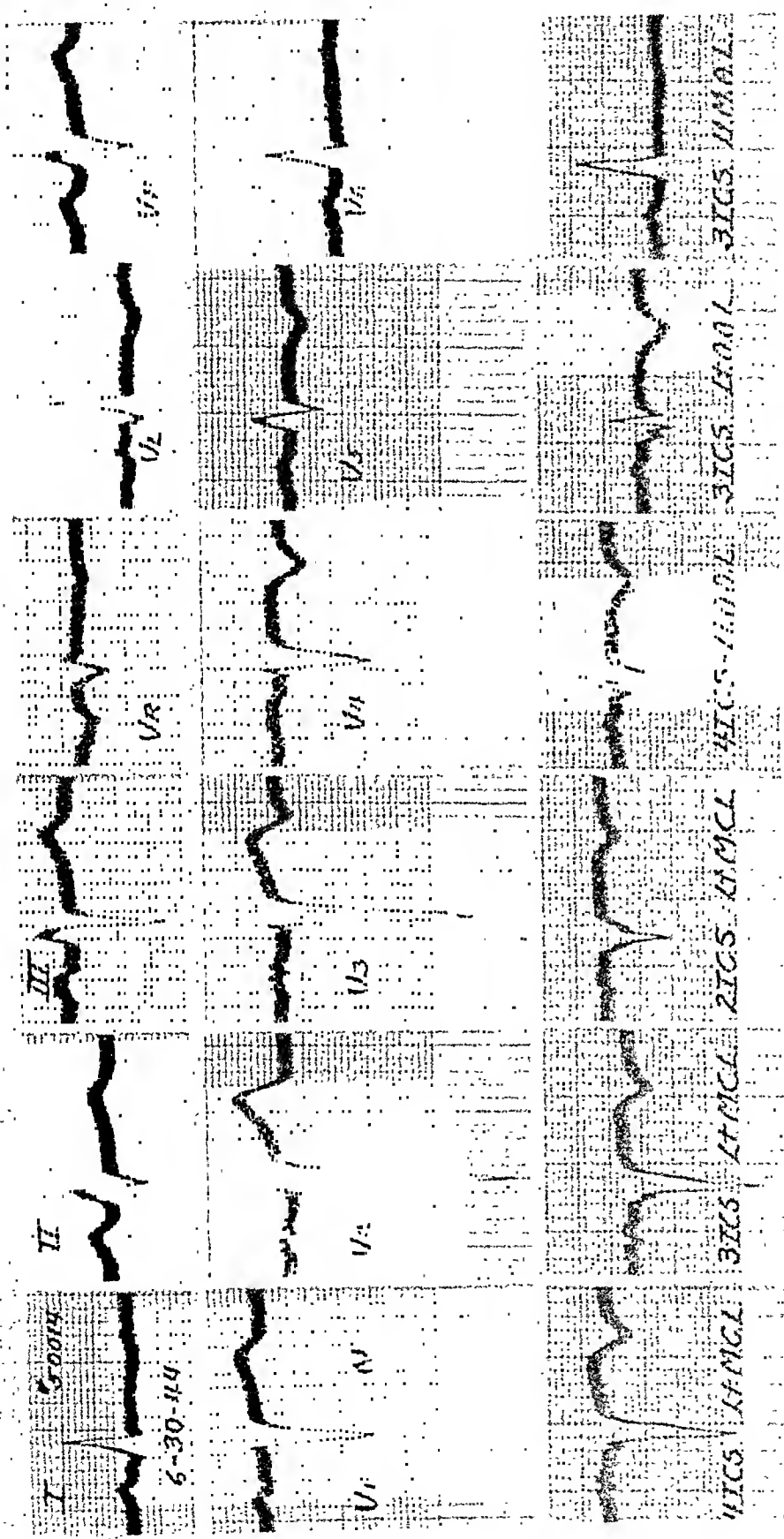


Fig. 1.—Case 1. High anterolateral infarction. Leads I and V₁, particularly the latter, display prominent Q waves and terminal inversion of the T deflections. The R deflection is conspicuously small in Lead V₂, and there is terminal inversion of T in Leads V₃, V₄, and V₅. The leads from the midclavicular line at the levels of the fourth, third, and second intercostal spaces exhibit large QS deflections and terminal inversion of T. Note also the prominent Q deflection and sharply inverted T wave in the lead from left anterior axillary line at the level of the fourth interspace. Symptoms strongly suggestive of infarction occurred in May, 1943.

radiated to the left arm and lasted twenty hours. He had been in a hospital for three weeks and was gradually resuming activity. There was no history of cardiac symptoms before the coronary accident.

There was no cardiac enlargement. The cardiac sounds were rather loud and the heart seemed overactive. There was a faint systolic murmur at the base. The blood pressure was 170/100.

The electrocardiograms made during the patient's acute illness were available and are reproduced along with the observations made at the time of our examination in Fig. 2. The tracing taken on the day of the attack (Jan. 5, 1944) displays very slight upward RS-T displacement in Lead I and slight downward RS-T displacement in Lead III, but is not certainly abnormal. On Jan. 11, 1944, the changes in the RS-T segment had become somewhat more distinct and a tiny Q wave had appeared in Lead I. The standard electrocardiogram taken eleven days later shows, in addition, definite terminal inversion of the T waves in Lead I, and upright T waves in Lead III. A single precordial electrocardiogram (IV) was made from a point said to be in the vertical line of V_3 but two intercostal spaces higher than the usual level; it displays QRS and T-wave changes characteristic of recent myocardial infarction. The records taken at the time of our examination on March 3, 1944, display only small Q waves in Leads I and V_L ; the usual precordial leads, V_1 to V_6 , are well within normal limits. The records made from a point high in the anterior axillary line and from a point in the line of Lead V_3 but at the level of the second intercostal space at the left sternal margin show prominent Q waves and normal T waves. These changes are regarded as residual electrocardiographic evidence of the infarction which had occurred two months earlier; apparently, the alterations of the T wave in this case were quite transient. It is notable that only the chest leads taken at higher levels and Lead V_L display signs which can be considered significant. The record from a point high in the midaxillary line does not show changes of similar degree.

CASE 3.—T. S., a 37-year-old chiropractor entered the University Hospital on Jan. 18, 1945, complaining of attacks of dyspnea and hemoptysis. Albuminuria and fluctuating hypertension had been discovered five years earlier, and one year prior to admission he began to have paroxysmal nocturnal dyspnea. He had a typical myocardial infarction in July, 1944, after which the attacks of paroxysmal left ventricular failure grew more severe and were precipitated by excitement and emotional stress.

The patient was a small, hyperkinetic man. Marked hypertensive retinopathy was present. The heart was tremendously enlarged. A moderately loud systolic murmur and a diastolic gallop sound were heard at the apex and along the sternum. There were frequent extrasystoles. The blood pressure was 190/130 in the right arm and 130/100 in the left arm. A difference of this order was consistently present and was not altered by the position of the arms. During periods of stress the blood pressure rose as high as 290/210. Conspicuous peripheral arterial thickening was present.

Slight albuminuria and moderate reduction of urea clearance were found. A histamine test failed to give a response suggestive of a pheochromocytoma.² Other laboratory studies of the blood chemistry and pyelograms were negative. Roentgenographic examinations of the thorax disclosed great cardiac enlargement and moderate pulmonary congestion.

A bilateral splachnicectomy was performed on Feb. 12, 1945. The operation and convalescence were uneventful. The patient was re-examined in the Heart Station on April 12, 1945. He was then generally improved, and the attacks of left ventricular failure were fewer

and less severe. The physical findings were not significantly different from those elicited prior to the operation. The blood pressure was 185/135. His referring physician recently informed us that he died on Aug. 8, 1945, from a cerebral hemorrhage.

Electrocardiograms made at the time of the acute infarction were available for review. On July 27, 1944, the standard leads displayed prominent Q waves,

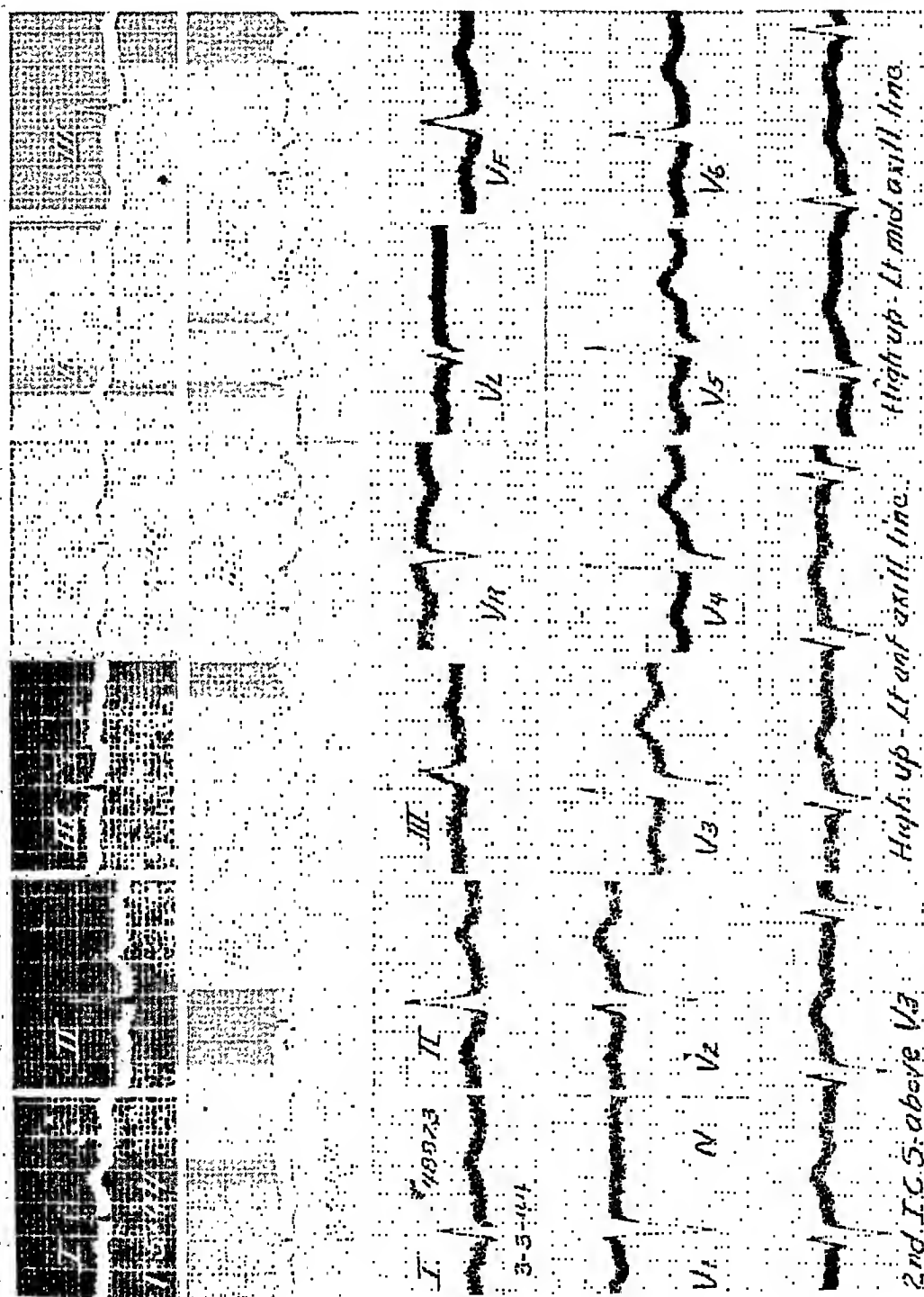


Fig. 2.—Case 2. High anterolateral infarction. Symptoms typical of infarction developed on Jan. 5, 1944. The record labelled "IV," which was taken on Jan. 22, 1944, was reported to have been taken by leading from a point two intercostal spaces above that specified for standard Lead IV; it displays changes in diagnostic of recent myocardial infarction. The tracings of March 3, 1944, show prominent Q waves in Lead I, Lead V1, and the leads from the upper levels of the left thorax. The ventricular complexes of the standard precordial leads (V1 to V6 inclusive) are well within normal limits.

slight elevation of the RS-T segment, and terminal inversion of the T waves in Leads I and II with marked depression of the RS-T segment in Lead III. The precordial leads showed unusual large QRS deflections with R waves which were definitely smaller in Lead V3 than in Lead V2 or V4, tiny Q waves in Leads V4, V5, and V6, and normal T deflections except for diphasic T waves in Lead V6.

Except for the relatively small R waves in Lead V_3 , the precordial leads did not suggest fresh myocardial infarction, although the standard leads were compatible with that diagnosis. The electrocardiograms, taken on Sept. 11, 1944, displayed the usual progression of changes in the standard leads. - The precordial leads on

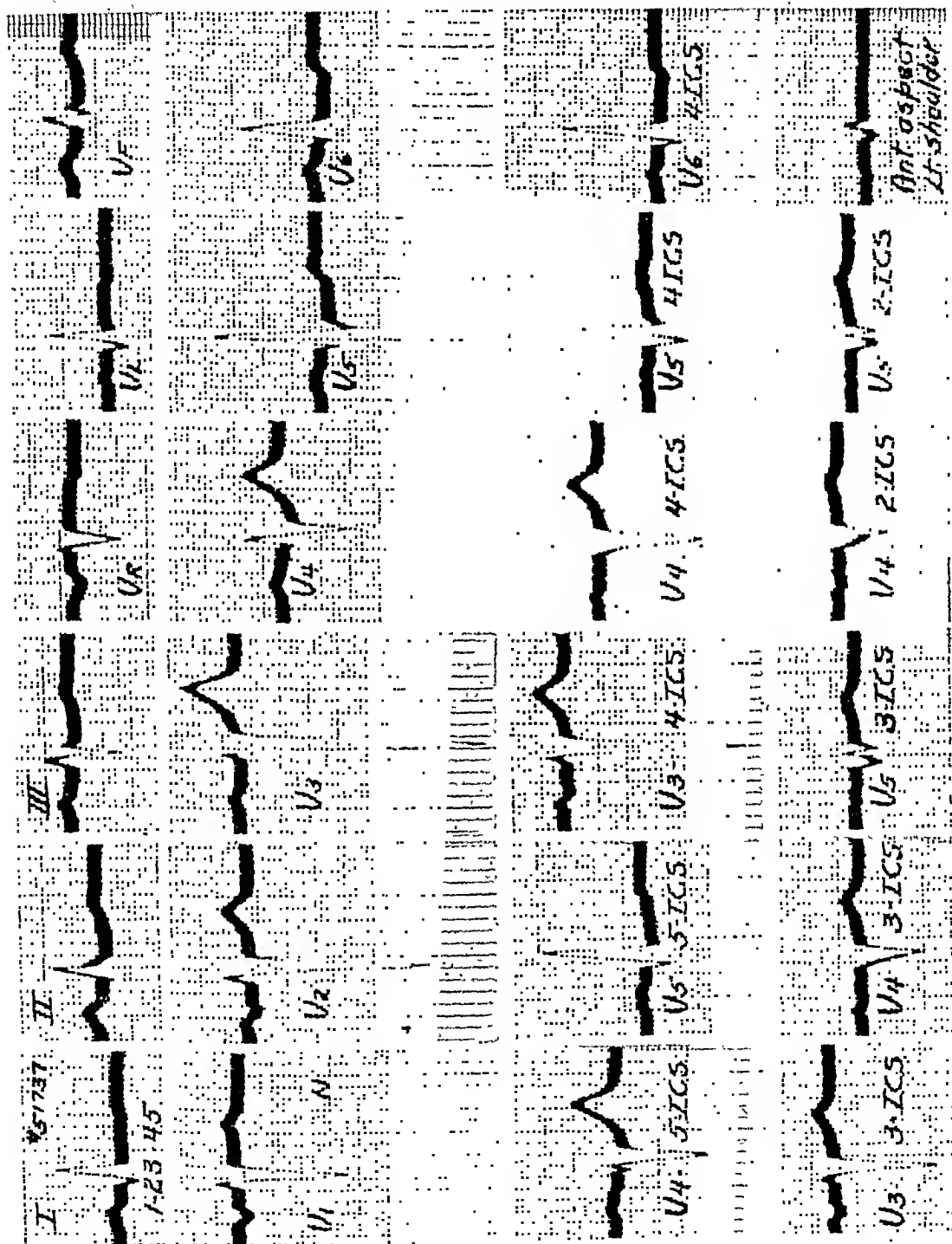


Fig. 3.—Case 3. High anterolateral infarction. The standard limb leads show prominent Q waves in Leads I and VI. The standard precordial leads are distinctly abnormal only as regards the small size of R in Lead V_3 . A number of the leads from the upper left chest display large Q or QS deflections which are strongly suggestive of infarction. The coronary accident occurred in July, 1941.

this occasion again showed a tiny R wave in Lead V_3 but, in addition, large QS deflections in Lead V_4 and deep, sharp, terminal inversion of the T waves in Leads V_5 and V_6 . The differences between the two sets of precordial leads may

have been due to differences in the locations of the precordial points selected on the two occasions or, what seems less likely, to changes in the size or character of the myocardial lesion.

Our own electrocardiograms were taken on Jan. 20, 22, and 23, 1945. All of the records are much alike and only the last set of tracings is reproduced (Fig. 3). Leads I and V_L show small Q waves and very slight terminal inversion of the T waves. There is slight depression of the RS-T segment in Leads II, III, and V_F , but this may be the result of digitalis therapy. The usual precordial leads display smaller R waves in Lead V_3 than in Lead V_2 or V_4 , tiny Q waves in Leads V_4 , V_5 , and V_6 and slightly inverted T waves in Leads V_5 and V_6 . Curves of this type may occur in left ventricular hypertrophy, but when they do the R wave usually grows progressively larger as the exploring electrode is moved to the left. Diminution of its size such as is seen here in Lead V_3 is rare in the absence of anterior infarction.¹ The implications of this finding become apparent when one examines the records taken at higher levels in the line of Leads V_4 and V_5 , for in these tracings there are large QS deflections very suggestive of infarction. As in Case 2, the inversion of the T waves previously present had cleared before the extensive electrocardiographic observations were made.

CASE 4.—W. T., a 55-year-old engineer was first seen in the Heart Station of the University Hospital on July 20, 1943. He complained of pain in the chest and calves. Five years before this, he had a quite typical myocardial infarction, and one year later he had similar but less severe symptoms. After the second attack he developed mild angina pectoris and intermittent claudication.

The patient was a short, stocky florid man. The heart was not enlarged. The cardiac sounds were rather distant. The blood pressure was 124/80. A few râles were heard at both lung bases posteriorly. No pulsations could be felt in the left posterior tibial or in either of the dorsalis pedis arteries.

The standard and unipolar limb leads (Fig. 4) display small Q waves in Leads II and V_F and prominent Q waves and inverted T waves in Lead III. The precordial leads show only flat or slightly inverted T waves in Leads V_5 and V_6 . In view of the previous clinical history, these changes may represent an old posterior myocardial infarct, but they are not of themselves diagnostic of this condition.

The patient returned to the Heart Station on Aug. 24, 1945. He had continued to have mild angina pectoris and intermittent claudication. Four months earlier, while walking in his factory, he had a sudden attack of severe dizziness and had to be assisted to his office. He noted diplopia for about one hour and a giddy sensation for several days. This latter complaint had persisted in mild degree up to the time of admission.

The findings on examination were much the same as on his initial visit. The blood pressure was 110/80. There was no evidence of postural hypotension. The hemoglobin, blood Kahn reaction, and miniature chest roentgenogram were normal.

The standard and unipolar extremity electrocardiograms (Fig. 4) are distinctly different from those taken two years earlier. There are small Q waves and flat T waves in Lead I, and the Q waves previously present in Leads II, III, and V_F have disappeared. Lead V_L exhibits prominent Q waves and sharp terminal inversion of the T waves. The usual precordial leads differ from those previously recorded in that the R waves failed to increase rapidly in size as the exploring electrode was moved to the left and the T waves are smaller. The

RS-T segment in Lead V₄ has a peculiar flattened outline and is somewhat depressed. Since these precordial records did not exhibit diagnostic evidence of infarction, leads from points at higher levels were employed. The records from

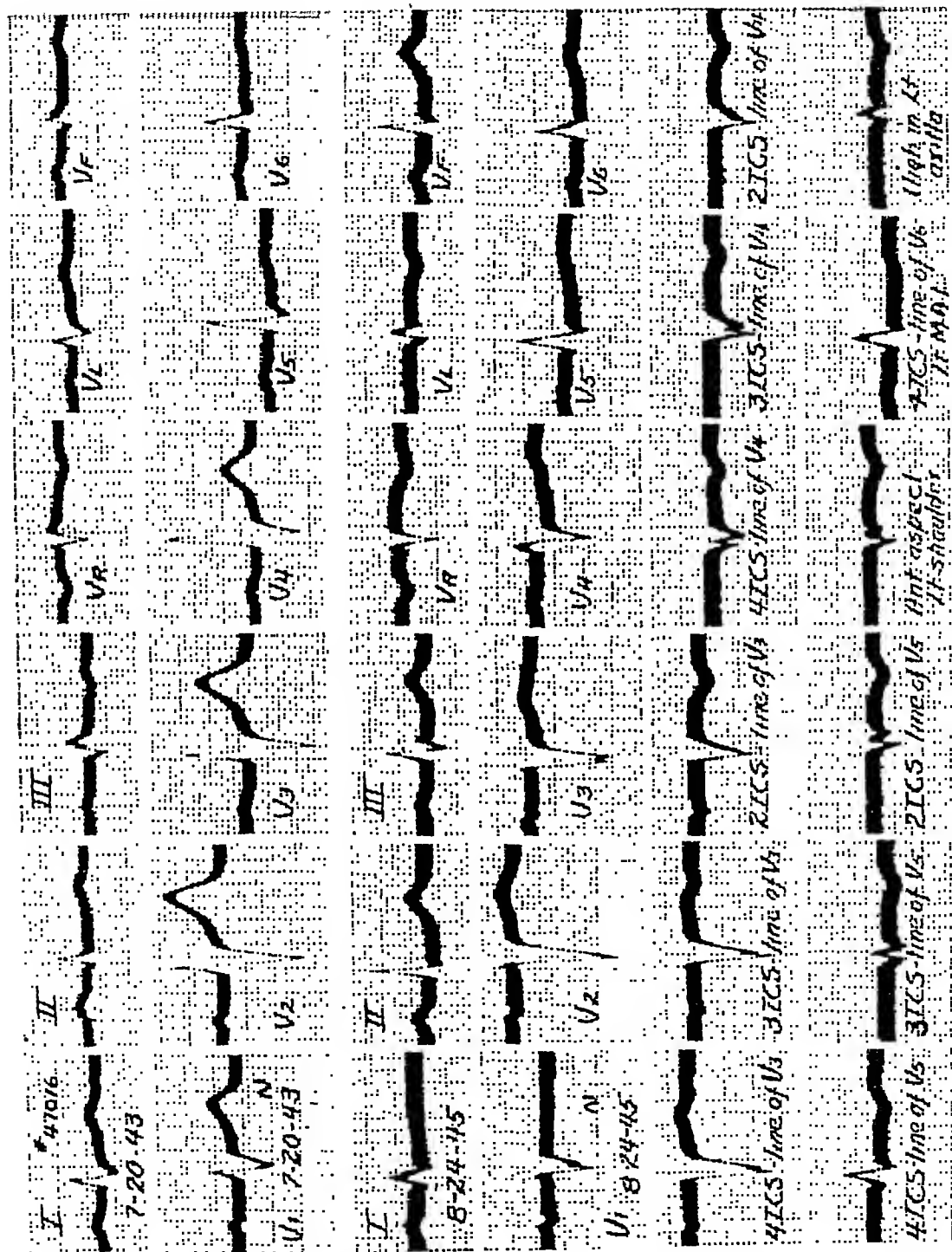


FIG. 4.—Case 4. Old posterior infarction plus high anterolateral infarction. The electrocardiograms taken on July 20, 1943, are strongly suggestive of old posterior infarction. There are prominent Q waves in Leads II, III, and V₆ and relatively large R and T deflections in the leads from the right side of the precordium. The electrocardiograms of Aug. 24, 1945, are very different; Lead V₄ shows prominent Q waves and terminal inversion of the T wave; many of the leads from the higher levels of the left thorax exhibit large Q or QS waves and terminal inversion of the T deflection. The standard precordial leads are negative apart from low-voltage T deflections and the small size of R in Leads V₂ and V₃. Symptoms suggestive of infarction occurred in 1938 and again in 1939.

points in the line of Lead V₄, but at the levels of the fourth, third, and second intercostal spaces at the sternum, and in the line of V₅ at similar levels, show changes in the QRS and T complexes which are in all respects characteristic of

myocardial infarction. Curves made from the midaxillary line at these higher levels do not display changes of like magnitude.

The date of the infarction responsible for the electrocardiographic changes recorded in 1945 is not clear. It may have occurred at the time of the severe

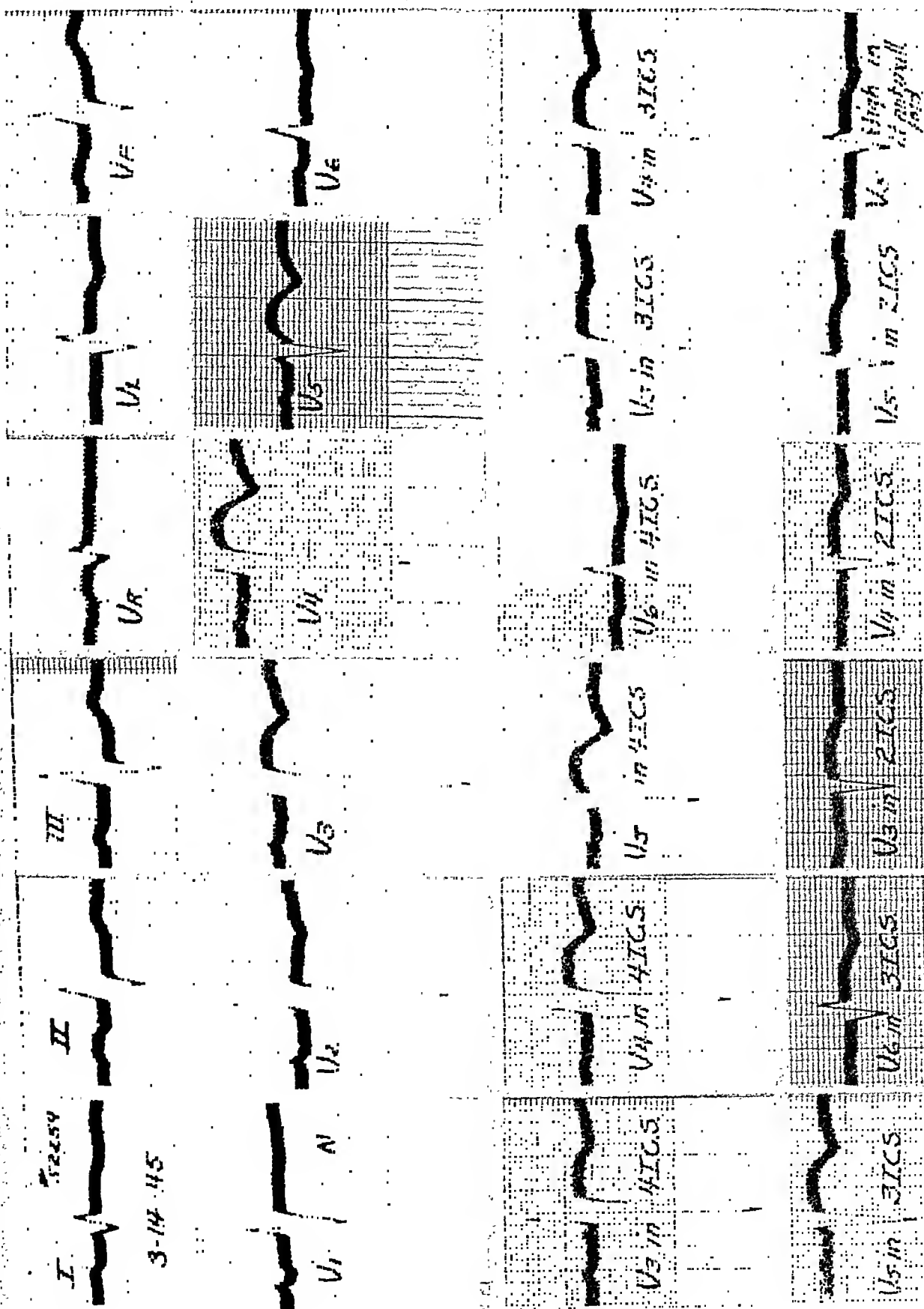


Fig. 5.—Case 5. High lateral infarction. The limb leads show large Q waves and terminal inversion of the T wave in Lead VI. The standard precordial tracings show abnormally small R deflections in Leads V₁ and V₂; there are changes in the RS-T segment and the T wave strongly suggestive of infarction in Leads V₃, V₄, and V₅. In a number of the leads from the higher levels of the left lateral thorax, similar changes in the T complex are combined with large Q or QS deflections.

attack of dizziness, or the patient may have regarded the symptoms associated with it as merely one of his many attacks of angina pectoris.

High Lateral Infarction.—One case is considered an example of high lateral infarction because the most striking electrocardiographic changes occurred in unipolar leads from the upper lateral aspects of the left thorax and left axilla.

CASE 5.—J. L., a 67-year-old tailor entered the University Hospital on March 4, 1945, complaining of dyspnea and visual difficulty. He had noted exertional dyspnea and intermittent ankle edema for many years. For one year there had been paroxysmal nocturnal dyspnea. Ten months before he was first seen, he had been in a hospital for ten days because of these complaints. There was no history suggesting an acute myocardial infarction. Cataracts had caused progressive reduction in vision.

The patient was moderately dyspneic and appeared chronically ill. Minimal pulmonary congestion and emphysema were noted. The heart sounds were normal; no murmurs were heard. The blood pressure was 140/84. There was peripheral arteriosclerosis and minimal pitting edema of the ankles. The urine, blood, stool, and blood Kahn examinations were negative. Roentgenographic examination of the thorax showed marked cardiac enlargement and slight pulmonary congestion.

The patient responded well to treatment for congestive cardiac failure. He was discharged on March 17, 1945. He returned for a cataract extraction on May 14, 1945. When last seen on Aug. 20, 1945, his condition was unchanged.

The standard limb and precordial leads taken on March 6 and March 13, 1945, are similar to those taken on March 14, 1945, which are reproduced in Fig. 5. In Lead I there are a tiny R wave preceding a deep S deflection, slight upward RS-T displacement, and slight terminal inversion of the T waves. Lead V_L is similar except for the absence of the small initial R. Leads II, III, and V_F show slight RS-T depression, possibly due to digitalis which the patient was receiving. The standard precordial curves are distinctly abnormal since the R wave grows progressively smaller in successive leads, becoming smallest in Lead V_5 . There is pronounced upward displacement of the RS-T segment in Leads V_3 , V_4 , and V_5 and terminal inversion of the T waves in Leads V_2 and V_6 in addition. Inasmuch as these changes were strongly suggestive of myocardial infarction, but did not include the presence of prominent Q or QS deflections in the leads from the usual precordial sites, additional tracings from points at higher levels were taken. The characteristic changes sought were recorded from regions high up in the line of Lead V_5 (see V_5 —2 I.C.S.) and in the vertical line of Lead V_6 (see V_6 —3 I.C.S.).

High Posterolateral Infarction.—One case has been classified as an example of high posterolateral infarction because the most characteristic electrocardiographic phenomena appeared in records taken from points high in the left posterior axillary line and over the left scapula. This case was unusually interesting because of the length of the interval which elapsed between the onset of symptoms and the appearance of the electrocardiographic changes. The patient recently developed a typical posterior myocardial infarct.

CASE 6.—J. A., a 46-year-old moulder, was admitted to the University Hospital on Sept. 16, 1944, complaining of severe retrosternal pain. Three years previously he began to have incapacitating intermittent claudication. On Sept. 10, 1944, he had attacks of severe, crush-

ing, retrosternal pain which radiated to the left arm and hand. These attacks were severe and prolonged and were only partially relieved by opiates. Five days before admission, the blood pressure was said to be 210/110.

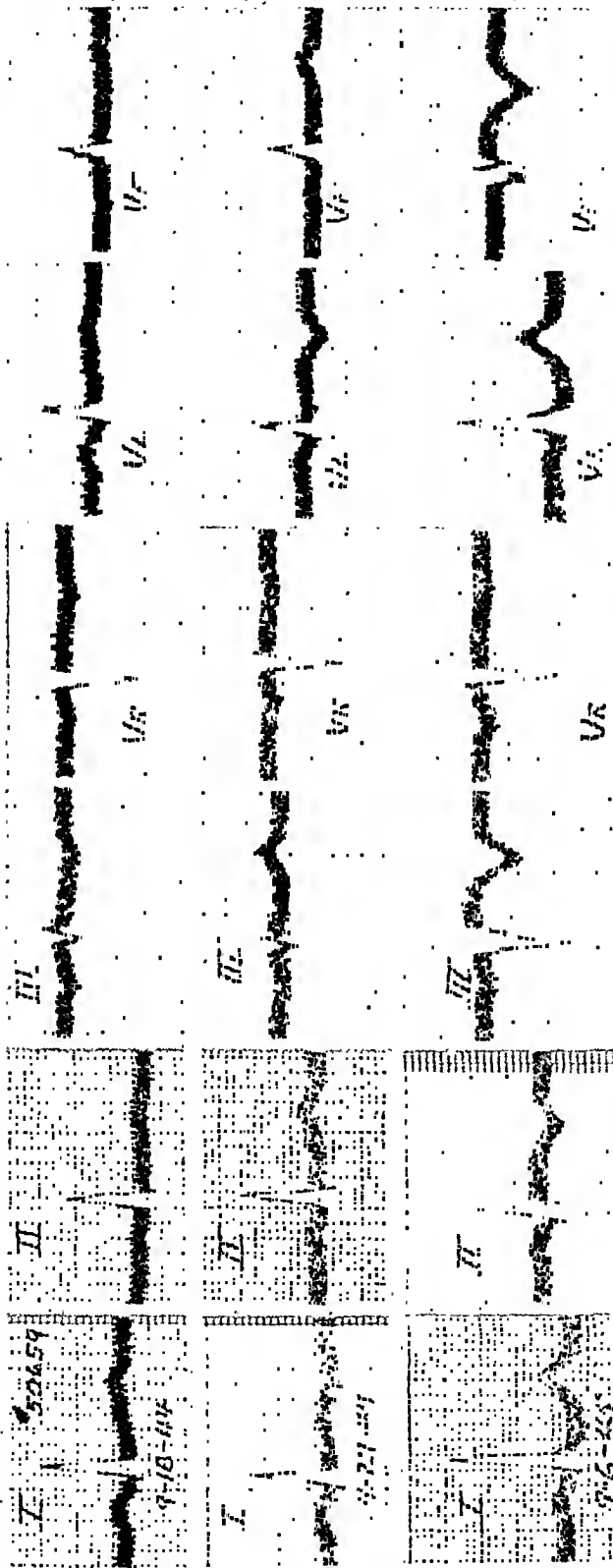


Fig. 6.—Case 6. High posterolateral infarction followed by posterior infarction. Standard unipolar limb leads. The tracings of Sept. 18 and Sept. 27, 1944, show delayed terminal inversion of the T deflection in Leads I and V1. The tracing of Sept. 6, 1945 is characteristic of recent posterior infarction. The first myocardial infarction occurred on Sept. 16, 1944; the second occurred on Sept. 4, 1945.

The patient was a heavy, muscular man and was in acute painful distress. The heart was not enlarged and the cardiac sounds were normal. The blood pressure was 150/90. The left leg was somewhat cool, and the pulse in the left dorsalis pedis artery was absent. The routine urine, stool, blood Kahn, chest roentgenographic, and blood examinations were negative except for slight leucocytosis during the first week in the hospital.

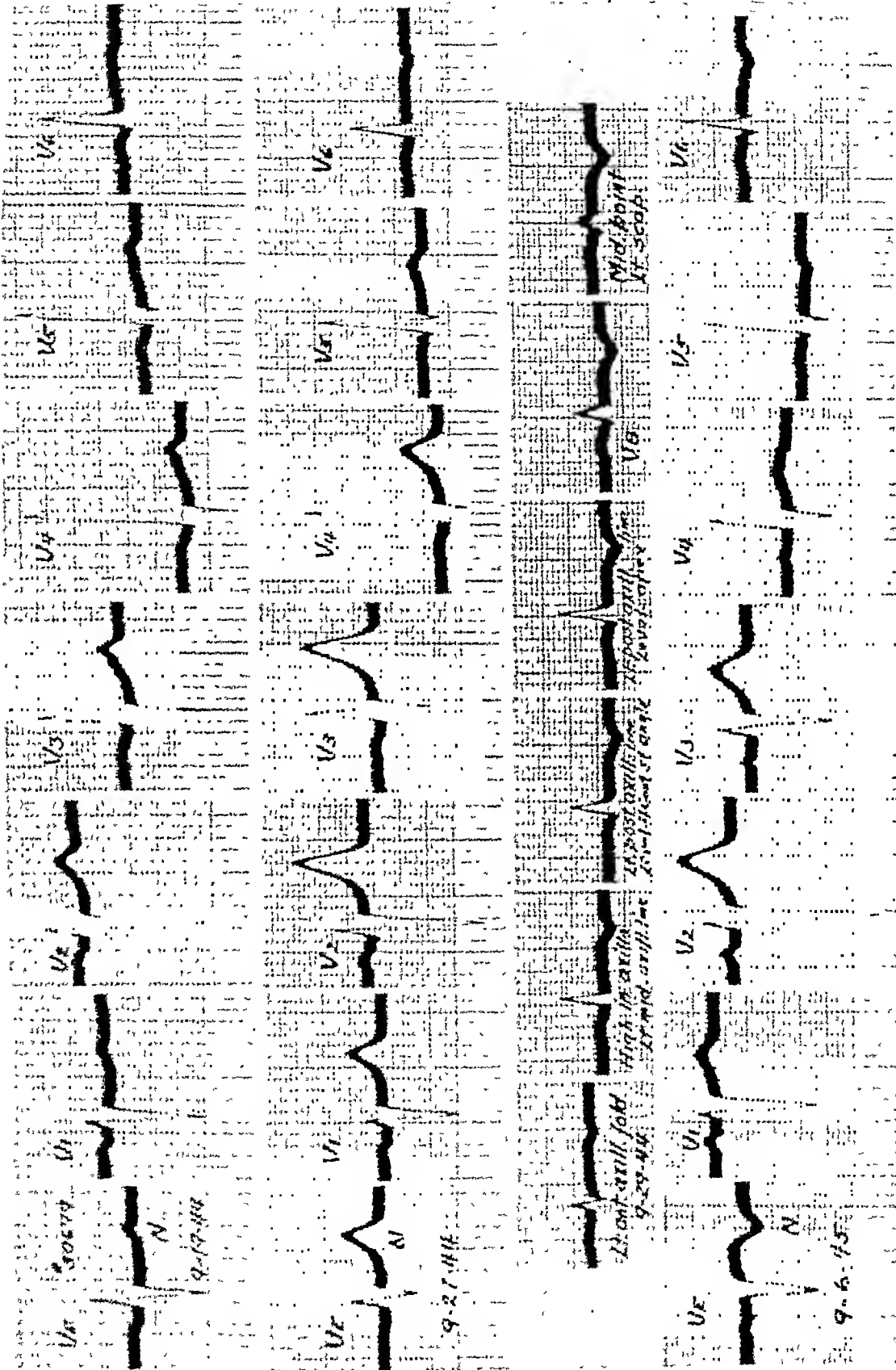


Fig. 7.—Case 6. High posterolateral infarction followed by posterior infarction. Precordial and other thoracic leads. The precordial leads taken on Sept. 27, 1944, illustrate the development of large pointed T waves in the leads from the right side of the precordium and of terminal inversion of the T wave in Lead V₄. More striking terminal inversion of the T deflection is exhibited by the leads from the higher levels of the left thorax. The tracings of Sept. 6, 1945, show sharp terminal inversion of T in Lead V₆ and less pronounced changes in the T complex in Leads V₃ and V₄.

The usual treatment for myocardial infarction was instituted. Two lesser attacks of pain occurred during the patient's stay in the hospital. There was some fever, maximum rectal temperature 103.2° F., during the first five days. The patient was discharged on the twenty-third hospital day.

A few of the records which display the progression of changes in this case are shown in Fig. 6. The standard and unipolar limb leads taken on Sept. 16, 1944, are not abnormal. The same leads taken on September 18 exhibit deflections of similar outline except for slight changes in the RS-T segment in Lead I and some flattening of the T wave in Lead II. The precordial leads of September 19 (Fig. 7) show a small depression of the RS-T segment in Leads V_1 and V_2 and very slight elevation of this segment in Lead V_6 , but these curves are not certainly abnormal. The standard and unipolar extremity leads of September 25 and September 27 are much alike and both display terminal inversion of the T waves in Leads I and V_L . The T waves in Leads II, III, and V_F have become very large, tall, and upright. Furthermore, the usual precordial tracings of September 27 are very different from those taken eight days earlier, for the T waves are much taller in the leads from the right side of the precordium and there is slight terminal inversion of the T wave in Lead V_6 . These changes represent the first unequivocal electrocardiographic evidence of the myocardial infarction which, judging from the clinical data, occurred at least ten days before they appeared. Additional records from points in the axilla, high in the mid-axillary line (Lt. mid. axill. line), in the posterior axillary line (Lt. post. axill. line Level—4 Cost. st. angle), and over the left scapula (Mid. point Lt. scap.) exhibit more characteristic changes in the T complex but no significant alterations of the QRS deflections (Fig. 7).

The patient was readmitted to the University Hospital on Sept. 4, 1945, complaining of severe pain in the chest. He had been comfortable except for mild angina pectoris until three days before when he had anginal pain lasting ten minutes. On the day of admission he had a very severe attack which persisted several hours despite repeated hypodermic injections.

The patient was slightly dyspneic. Fine râles were heard at the bases of both lungs. The heart was slightly enlarged and some precordial tenderness was noted. The blood pressure was 132/70. The blood, urine, stool examinations, and the circulation time were normal.

The patient was again treated for myocardial infarction in the usual manner. There was some recurrence of pain during the third week, but the hospital course was not otherwise remarkable. He was discharged on the twenty-sixth day.

The standard and unipolar limb leads of Sept. 5, 1945, are characteristic of recent posterior myocardial infarction and show prominent Q waves and deep terminal inversion of the T waves in Leads II, III, and V_F (Fig. 6). Records taken on September 6 and September 21 are similar except for greater inversion of the T deflections. The precordial leads (Fig. 7) are similar to those taken on Sept. 27, 1944, except that terminal inversion of the T waves is present in Leads V_5 , V_6 , and V_E . Leads from points low in the left posterior axillary line also show typical T-wave changes but those from points at higher levels, which exhibited significant changes after the first infarction, fail to show such alterations. The contrast of changes in Leads V_L and V_F produced by the two infarcts and the appearance with the second infarction of deep inversion of the T waves in the lead from the ensiform cartilage (V_E) are additional features of interest.

DISCUSSION

Wood, Wolferth, and Bellet³ have proposed criteria for the electrocardiographic diagnosis of acute lateral or midventricular infarction. The features which they considered important were depression of the RS-T segment in Lead IV, and usually in Leads I and II, and the absence of signs of posterior infarction in Lead III. Using these criteria Thomson and Feil⁴ reviewed the electrocardiograms of nineteen patients who were found at post-mortem examination to have lateral myocardial infarction. Their studies did not disclose a consistent correlation between the post-mortem and the electrocardiographic findings; only four of nine patients with recent lateral infarction showed the pattern described by Wood, Wolferth, and Bellet. Boseo⁵ has employed the same criteria in an effort to establish lateral infarction as a distinct anatomicoclinical entity different from infarction involving the anterior or posterior walls of the left ventricle. It has been recognized^{3,4} that changes of this same type may result from digitalis, may occur in records made during attacks of angina pectoris, and may appear under other circumstances. Wilson⁶ has pointed out that the most reliable signs of myocardial infarction consist of a sequence of characteristic alterations in both the QRS and T complexes. It has been our experience in this laboratory that lateral infarction of the more usual variety produces these characteristic changes in unipolar precordial leads from the left lateral thorax (Leads V₃, V₆, and V₇, which is from the posterior axillary line) at the level of the cardiac apex.¹ The records of the group of cases presented in this report are quite different from those of the more usual examples of lateral infarction, and we believe that they represent an important, although probably somewhat uncommon type of lateral myocardial infarction.

If the electrocardiographic observations made in these six patients are reviewed, certain features appear to be significant. The standard electrocardiograms of all but one of the patients show tiny or small Q waves and flat or slightly inverted T waves in Lead I. The magnitude of the changes in the T complex varies from case to case, but this would be expected since the electrocardiographic studies were made at very different stages of the infarction in the different instances. Although there are no Q waves in Lead I in the records of Case 5 which are reproduced, they were present in tracings taken earlier. This difference may be accounted for by a shift in the position of the heart. The ventricular complexes of the unipolar lead from the left arm (V_L) are similar in general outline to those of Lead I in all cases and exhibit small Q waves and flattening, slight inversion, or sharp terminal inversion of the T deflections. On the whole, the changes in Lead V_L are more striking than those in Lead I, and, in the instance of high lateral infarction (Case 5), the difference is pronounced, probably because the zone of infarction was in such a position as to face toward the left shoulder as well as toward the upper left axilla.

The character of the complexes of the standard precordial leads distinguishes these cases from the usual type of lateral infarction. There are no changes diagnostic of infarction in the QRS complexes of the leads from the left side of the precordium, and, in all but two cases (1 and 5), distinctive altera-

tions in the T complex are absent in the leads from this region. On the whole, the deviations from the normal in the standard precordial leads were least impressive in the cases of high anterolateral infarction. In one instance (Case 2) these leads are normal, in two (Cases 3 and 4) they show only tiny Q waves and minor changes in the T waves of the leads from the left side of the precordium, and in the remaining one (Case 1) the R waves are unusually small in all of these leads. Terminal inversion of the T waves is also seen in Leads V_4 and V_5 in this case. The usual precordial leads in the case of high lateral infarction (Case 5) display a pronounced decrease of the height of the R wave in successive leads. This case exhibits slight to moderate inversion of the T waves and some upward displacement of the RS-T segment in the leads from the left side of the precordium. This displacement is apparently of the persistent type since the clinical data do not suggest that the infarction was recent. There were, however, no roentgenographic signs of ventricular aneurysm, such as have been observed in some instances of persistent displacement of the RS-T segment.⁷ In the single instance (Case 6) of high posterolateral infarction, the usual precordial leads showed at first only slight depression of the RS-T segment in Leads V_1 and V_2 . Subsequently when the changes in other leads had become apparent, the T waves of the leads from the right side of the precordium became taller and slight terminal inversion of the T deflection appeared in Lead V_6 .

So far as the supplementary leads taken from the upper left thorax are concerned, it may be said that, in all but one instance (Case 3), Q or QS and T-wave changes characteristic of myocardial infarction were recorded. In the single exception, only QRS changes were present, presumably because the infarction had occurred six months before. Earlier records of the usual type displayed characteristic alterations in the T wave. It was necessary to place the exploring electrode one to three intercostal spaces above the usual levels to obtain diagnostic electrocardiographic changes. In some instances (Case 6) the zone which yielded the most significant changes was relatively small whereas in others (Cases 1 and 4) it was much larger. This difference may have depended upon the relative size of the infarcted region, but we have no evidence bearing on this question. The distinction between anterolateral, lateral, and posterolateral infarcts is here based upon the position of the vertical lines through the points which yielded the most pronounced electrocardiographic changes. If the most pronounced evidence of infarction occurred in leads from points lying directly above those used in taking Leads V_3 , V_4 , and V_5 , the case was put in the first group; if it occurred in leads from points above those used in taking Leads V_5 and V_6 , it was placed in the second; and if it occurred in leads from points in the left posterior axillary line (V_7) and the left scapular line, it was placed in the third group.

Our experience with electrocardiograms obtained by means of unipolar leads from the higher levels of the chest has been rather limited. In order to control the observations made in our cases of high lateral infarction, we have examined tracings* obtained in a similar way from a small group of normal subjects and

*Some of the tracings utilized were taken in this laboratory⁸; others were taken by Miss Annie Mary Lyle of the Prudential Insurance Company.⁹

from a group of patients with various kinds of electrocardiographic abnormalities. Prominent Q or QS waves were not encountered in leads from the higher levels of the left anterolateral and lateral thoracic areas when the heart was normal. In general, the ventricular complexes of leads from the higher levels of the left anterolateral and lateral thoracic areas are transitional in form between those of the standard unipolar lead from the left side of the precordium and those of the unipolar lead from the left arm (Lead V_L). Whenever, for any one of a variety of reasons, there are large Q waves or QS deflections in Lead V_L , prominent Q waves will usually be present in some leads from the upper levels of the left thorax. It is, therefore, our present opinion that prominent Q waves, QS deflections, and sharply inverted T waves in Leads of the kind in question have an important bearing upon the diagnosis of myocardial infarction only when they give rise to ventricular complexes which are more typical of this lesion than the ventricular complexes of either the standard precordial leads or the unipolar lead from the left arm. The chief indication for additional leads from the upper levels of the left thorax is the presence of changes suggestive of infarction in Lead V_L without corresponding changes in the standard leads from the left side of the precordium.

There are several possible explanations for the occurrence of the most striking signs of infarction in leads from thoracic levels above those usually explored. We believe that this phenomenon is usually due to infarction of parts of the wall of the left ventricle which are closer to the base of this chamber than those more commonly involved. Some of the infarcts studied by Thomson and Feil⁹ seem to have been of this sort, and we have recently heard of instances of high lateral infarction demonstrated at autopsy in which the standard extremity and precordial electrocardiograms resembled some of those described in this article.¹⁰ It is, of course, possible that the peculiarities of the electrocardiographic patterns we have described are sometimes the result of rotation of the heart or some other change in the spatial relations of its surfaces to the standard electrocardiographic leads. It is also difficult to predict what modifications of the more common electrocardiographic patterns produced by infarction might arise as a consequence of ventricular enlargement following a coronary accident.

The delayed appearance of electrocardiographic evidence of myocardial infarction in Case 6 (Figs. 6 and 7) is, perhaps, deserving of comment. The clinical findings were sufficiently characteristic at the time of the patient's first admission to the hospital to justify the diagnosis made, but supportive electrocardiographic data were not obtained, despite frequent examinations, until ten days later. Some considerations which may account for the delayed appearance of electrocardiographic signs of infarction have been discussed elsewhere.¹¹ It has been pointed out that in leads from the precordium and extremities, in contrast to leads from the surface of the heart itself, the effects produced by the parts of the infarct responsible for RS-T displacement may obscure those produced by the muscle responsible for inversion of the T deflection. This is likely to happen when the muscle zone ischemic enough to give rise to changes of the first kind in direct leads is approximately equal in size to the zone ischemic only to the degree necessary to give rise to changes of the second kind. A loca-

tion of the infarcted region which is unfavorable with respect to the leads employed may also account for the late appearance of characteristic electrocardiographic evidence of infarction. Finally, the extension of an initially small infarct may explain the apparently late development of electrocardiographic changes in some instances. In the case under consideration the location of the infarct was unusual and certainly unfavorable as far as its detection by means of the usual extremity and precordial leads was concerned. It seems probable, however, that the factor first mentioned was an important cause of the late appearance of inversion of the T wave in Leads I, V_L , and V_6 .

SUMMARY

Six cases of suspected infarction of the basal parts of the lateral wall of the left ventricle are reported. The usual unipolar limb leads and the six standard precordial leads failed to furnish unequivocal evidence of myocardial infarction in these cases. Unipolar leads from points on the anterolateral, lateral, and posterolateral aspects of the upper left thorax supplied electrocardiographic data of greater diagnostic value.

The types of lesions differentiated have been classified as high anterolateral, high lateral, and high posterolateral infarcts on the basis of the vertical lines in which the most significant electrocardiographic changes were recorded.

The opinion is expressed that in these instances the electrocardiographic changes typical of infarction were most pronounced in leads from the upper left thorax because the infarcted region was more basal and more lateral than is usually the case. It is, however, admitted that rotation of the heart or some other change in the relations of its surfaces to the usual leads may have been responsible for some of the electrocardiographic peculiarities encountered.

It is recommended that unipolar leads from the higher levels of the left thorax be taken when the clinical history and Lead I, or Lead V_L , both suggest that myocardial infarction has occurred and the standard leads from the left side of the precordium fail to display changes of the kind and magnitude expected.

REFERENCES

1. Wilson, F. N., Johnston, F. D., Rosenbaum, F. F., Erlanger, H., Kossman, C. E., Hecht, H., Cotrim, N., Menezes de Oliveira, R., Scarsi, R., and Barker, P. S.: The Precordial Electrocardiogram, *AM. HEART J.* 27: 19, 1944.
2. Roth, G. M., and Kvale, W. F.: A Tentative Test for the Diagnosis of Pheochromocytoma, *J. Lab. & Clin. Med.* 30: 366, 1945.
3. Wood, F. C., Wolferth, C. C., and Bellet, S.: Infarction of the Lateral Wall of the Left Ventricle: Electrocardiographic Characteristics, *AM. HEART J.* 16: 387, 1938.
4. Thomson, H. W., and Feil, H.: Infarction of the Lateral Wall of the Left Ventricle. Pathologic and Electrocardiographic Study, *Am. J. M. Sc.* 207: 588, 1944.
5. Bosco, G. A.: *Síndrome Coronario Lateral*, Buenos Aires, 1943, Imprenta Ferrari Huos.
6. Wilson, F. N.: *Diseases of the Coronary Arteries and Cardiac Pain*, Edited by Robert Levy, New York, 1936, The Macmillan Company, p. 281.
7. Rosenbaum, F. F., Johnston, F. D., and Alzamora, V. V.: Persistent Displacement of the RS-T Segment in a Case of Metastatic Tumor of the Heart, *AM. HEART J.* 27: 667, 1944.
8. Rosenbaum, F. F., and Wilson, F. N.: Unpublished observations.
9. Lyle, A. M.: Personal communication to F. N. Wilson.
10. Myers, G. B.: Personal communication to F. F. Rosenbaum.
11. Wilson, F. N., Rosenbaum, F. F., and Johnston, F. D.: The Interpretation of the Ventricular Complex of the Electrocardiogram, *Advances in Internal Medicine*, II, New York, Interscience Publishing Co. In press.

THE DEMONSTRATION OF VENTRICULAR SEPTAL DEFECT BY MEANS OF RIGHT HEART CATHETERIZATION

ELEANOR DEF. BALDWIN, M.D., LUCILLE V. MOORE, M.D., AND
ROBERT P. NOBLE, M.D.
NEW YORK, N. Y.

WITH THE TECHNICAL ASSISTANCE OF
MICHAELEEN PATTERSON, B.A., AND DORIS M. HARNSEBERGER, B.S.

ISOLATED ventricular defects are not uncommon. Maude Abbott¹ listed 50 pure ventricular defects in her series of 1,000 congenital cardiac lesions. The clinical diagnosis of this condition has been entirely dependent upon the presence of the pathognomonic Roger murmur,² a localized loud blowing systolic murmur heard best just to the left of the mid-sternum and often accompanied by a palpable thrill. Presumably the size of the defect is in inverse proportion to the loudness of the murmur. An associated cardiac enlargement may be present. The electrocardiogram is frequently normal, although right axis deviation and a prolongation of the auriculoventricular conduction time are not uncommon. Since the shunt is arteriovenous, cyanosis is not present, except rarely as a terminal manifestation. Therefore, many ventricular septal defects are not recognized during life but are found only at necropsy.

The development of a safe and relatively simple technique for the catheterization of the right heart in man³ presents a new diagnostic aid admirably adapted for the detection of this particular congenital defect. Following the introduction of a catheter into the right heart, samples of blood may be withdrawn from various known areas by determining the position of the tip of the catheter by fluoroscopy. The presence of an arteriovenous shunt may then be demonstrated by the comparison of the respiratory gas contents of these blood samples with one another and with samples of arterial blood. Further information on the hemodynamics may be obtained by connecting the intracardiac catheter to a recording type of manometer, such as the one described by Hamilton⁴ and analyzing the resultant pressure tracings. Finally, by direct observation of the movements of the catheter within the right heart, useful impressions as to the size, shape, and location of the chambers of the heart may be acquired which supplement the information obtained from the routine x-ray and fluoroscopic studies. In such a study, however, two prerequisites must be met which limit its usefulness in children: (1) The peripheral venous system must be sufficiently developed to allow the easy passage and subsequent manipulation of at least a No. 8, preferably a No. 9 catheter

From the Departments of Medicine and Physiology of the College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital.
Received for publication Nov. 19, 1945.

into the median basilic vein, and (2) enough passive cooperation of the subject must be assured to maintain a relatively steady physiologic state throughout the procedure, since it is quite obvious that the circulation will vary enormously from minute to minute in an apprehensive, restless, and uncomfortable subject.*

Hemodynamic studies made upon two subjects with congestive circulatory failure of obscure etiology will be presented in this report. A ventricular septal defect was demonstrated in both cases.

PROCEDURE

The subject was brought to the laboratory in the morning under basal conditions. He was given 30 mg. of phenobarbital by mouth just before leaving the ward. The radiopaque catheter was passed through the median basilic vein into the thorax under fluoroscopic vision, and the tip was manipulated into the desired position.³ Blood samples were withdrawn under oil; a rigid air-free technique was observed. Pressure recordings were made in both the right auricle and ventricle. Simultaneous blood samples were taken from the ventricle, and from the femoral artery through an indwelling needle. These samples were immediately analyzed for their oxygen and carbon dioxide content in a Van Slyke manometric apparatus.⁵ In one case in which the expired air was collected, aliquots of this air were analyzed for their oxygen and carbon dioxide content in a Haldane gas burette. The tracings of the pressures within the right ventricle, auricle, and peripheral veins were recorded by a Hamilton manometer which was calibrated after each recording.⁶

From this series of observations, information was obtained as to the presence or absence of an arteriovenous shunt, the peripheral blood flow, and the pressure gradient between the peripheral veins, the right auricle, and the right ventricle.

The demonstration of arterialization of the right ventricular blood is proof of an interventricular arteriovenous shunt which cannot be questioned if arterial blood is withdrawn from the catheter. Except in the presence of an additional tricuspid insufficiency, in which condition the auricular as well as the ventricular blood will be arterialized, a ventricular septal defect can be detected by a significant difference between the respiratory gas content of the auricular as compared with the ventricular blood samples. It is, therefore, of importance to determine what degree of difference may be considered to be significant. Stead and his co-workers⁷ have reported that, in three subjects, blood taken from the auricle in the region of the tricuspid valve was found to have a very low oxygen content compared with samples taken from the right ventricle or other parts of the auricle. They concluded that the catheter had entered the coronary sinus or an aberrant hepatic vein. Cournand et al.,³ on the other hand, have shown that the oxygen content of blood taken successively from the right ventricle and auricle close to the tricuspid valve varied 0.3 volume per cent or less in 19 of 22 subjects, and that in only one subject was the difference greater than 1 volume per cent. Thus, a variation of oxygen content of more than 2

*Since this article was written, Cournand and his group at Bellevue Hospital have studied several young children between 2½ and 6 years of age with various congenital heart defects, using avertin as a basal anesthetic and introducing a No. 7 catheter into the heart through the saphenous vein, exposed at the femoral area under local anesthesia.

volumes per cent between the ventricular and auricular samples may be considered a significant difference denoting an abnormal communication. Since the carbon dioxide content of the mixed venous blood tends to vary considerably from minute to minute with any slight respiratory or circulatory change, variations between the carbon dioxide content of the several samples are confirmatory but not reliable evidence of an abnormal shunt. Furthermore, if the subject under study is in severe right-sided cardiac failure, a functional tricuspid insufficiency must be suspected and looked for, and, if found to be present, it must enter into the evaluation of the data.

In the absence of a tricuspid insufficiency or an abnormal shunt, the oxygen content difference between the arterial and mixed venous blood within either the auricle or ventricle is a measure of the systemic blood flow. In the normal resting individual this difference is 4.5 ± 0.7 volumes per cent, but in congestive failure or shock it may be increased to as high a value as 16 volumes per cent,^{8, 9} and, conversely, during anxiety, anemia, or fever, to as low as 2.5 volumes per cent.^{10, 11} If the total oxygen consumption per minute is known during the period of blood sampling, the systemic blood flow may be calculated, using the simple Fick principle:

$$\text{Systemic blood flow/min.} = \frac{\text{Oxygen intake ml. per minute}}{\text{Arterial O}_2 \text{ vol. \%} - \text{venous O}_2 \text{ vol. \%}}$$

Since the volume of blood flowing through the ventricular septal defect is unknown, the pulmonary blood flow obviously cannot be calculated in the presence of this condition, unless samples are taken in the pulmonary artery.

The analysis of the pressure tracings is primarily dependent upon an unobstructed manometric system. It is often of great value to know the pressure changes at the site of the blood sampling. For example, if the ventricular blood is identical with that drawn from the femoral cannula, a comparison of the pressure tracings will determine whether or not the catheter tip has penetrated from the right into the left ventricle through the defect. Furthermore, an auricular pressure tracing is the most accurate means for the detection of a tricuspid insufficiency.⁶

OBSERVATIONS ON TWO PATIENTS

With this preliminary discussion of the interpretation of the hemodynamic observations made possible by right heart catheterization, the case reports and cardiac catheterization studies of two subjects with ventricular septal defects will be presented.

CASE 1.—A. S., a 20-year-old single girl of Italian parentage, gave a history of a fall at the age of 7 years in which she struck her epigastrium against a step. Following this accident she was admitted for abdominal swelling to another hospital, where a diagnosis of rheumatic heart disease was made. After four months the abdominal swelling subsided and she was symptom-free until the age of 15 years, at which time swelling of her ankles was followed by enlargement of her abdomen. For the six months preceding admission to the Presbyterian Hospital, her edema did not respond to treatment. Physical examination disclosed a poorly developed, pale adolescent girl appearing much younger than her chronological age, with a greatly distended abdomen. There were distention and pulsation of the jugular veins. The lips and nail beds were slightly cyanotic. The heart was enlarged more to the right than to

the left. Over the pulmonary conus there was marked pulsation, a systolic murmur transmitted to the clavicular area, and a diastolic murmur transmitted to the apex. There was a loud systolic murmur over the apex and tricuspid area. The pulmonic second sound was louder than the aortic. The abdominal wall was edematous and an obvious fluid wave could be demonstrated. Pitting edema of the sacrum, shins, and ankles was present. On admission, the venous pressure was 240 mm. of water. Serum proteins were 6.1 Gm., albumin, 4.4 per cent, and globulin, 1.7 per cent. Other laboratory findings were noncontributory. Fluoroscopy of the chest revealed moderate enlargement of the heart with good pulsation at the left and only transmitted pulsation at the right border. After ingestion of barium, a posterior displacement of the esophagus was noted. The electrocardiogram disclosed a left-axis deviation and a P-R interval of 0.27 second. Clinically, she was considered at this time to have an adhesive pericarditis associated with possible chronic rheumatic valvular disease. The possibility of a congenital cardiac lesion was suggested by one examiner.

The hemodynamic studies were carried out on the ninth day following her hospitalization, after diuresis had brought about a 14-pound weight loss.



Fig. 1.—Roentgenogram of the thorax in Case 1, A. S.

Procedure (Figs. 1 and 2; Tables I and II).—The catheter passed readily into the right auricle, which appeared to be neither dilated nor enlarged, and easily slipped through the tricuspid valve into a markedly enlarged right ventricle. Simultaneous blood samples taken from the right ventricle and femoral artery disclosed almost identical values for the respiratory gas contents: a carbon dioxide content of 50.5 volumes per cent and an oxygen content of 15.6 volumes per cent in the ventricular blood, and a carbon dioxide content of 50 volumes per cent and an oxygen content of 15.8 volumes per cent in the femoral arterial blood. This was a completely unexpected occurrence, which was positive proof

AMERICAN HEART JOURNAL

TABLE I. BLOOD GAS MEASUREMENTS

(A. S. [Case 1], female, 20 years old, oxyhemoglobin capacity 17.1 volumes per cent)

TIME	LOCATION OF CATHETER TIP	CARBON DIOXIDE CONTENT (VOLS. %)	OXYHEMOGLOBIN CONTENT (VOLS. %)	PRESSURE (MM. HG)	OXYHEMOGLOBIN SATURATION (%)
11:20 A.M.	Posterior right ventricle	50.1	15.4	40/10	90.0
11:21 A.M.	Femoral cannula	50.0	15.6	112/72	90.8
12:50 P.M.	Anterior right ventricle	50.8	14.4	40/10	83.2
2:30 P.M.	Right auricle at tricuspid valve	51.2	14.1	mean 9.8	82.5
2:45 P.M.	Right auricle at level of third rib	52.4	10.4	mean 9.8	60.8
3:00 P.M.	Right auricle at 4 cm. higher	52.5	10.7	mean 9.8	62.5



Fig. 2.—Lateral roentgenogram of the thorax in Case 1, A. S., showing the catheter in place in the right ventricle. The second ventricular blood sample and ventricular tracings were obtained with the catheter in this position.

TABLE II. BLOOD PRESSURE MEASUREMENTS

(A. S. [Case 1], pressures recorded in millimeters of mercury)

PRESSURES	FEMORAL ARTERY	RIGHT VENTRICLE	RIGHT AURICLE	PERIPHERAL
Systolic	112	43-33		
Diastolic	72	16-10	9.8	9.8
Mean	90	27-23		
Pulse	40			

of a septal defect. While awaiting the afore-mentioned determinations, simultaneous femoral and right ventricular pressure tracings were recorded without changing the position of the catheter. It was very evident from these pressure tracings that the catheter tip had not entered the left ventricle, since the femoral arterial pressure was 112/72 and the right ventricular pressure was 40/10. When the results of the blood gas analysis were known, the catheter was widely manipulated. The right ventricle was observed to extend from about 1 cm. below the sternum (Fig. 2) to within a centimeter or two of the vertebral column. A second ventricular sample taken from the anterior area of the right ventricle disclosed a carbon dioxide content of 50.8 volumes per cent and an oxygen content of 14.6 volumes per cent, thus showing an admixture of mixed venous blood.

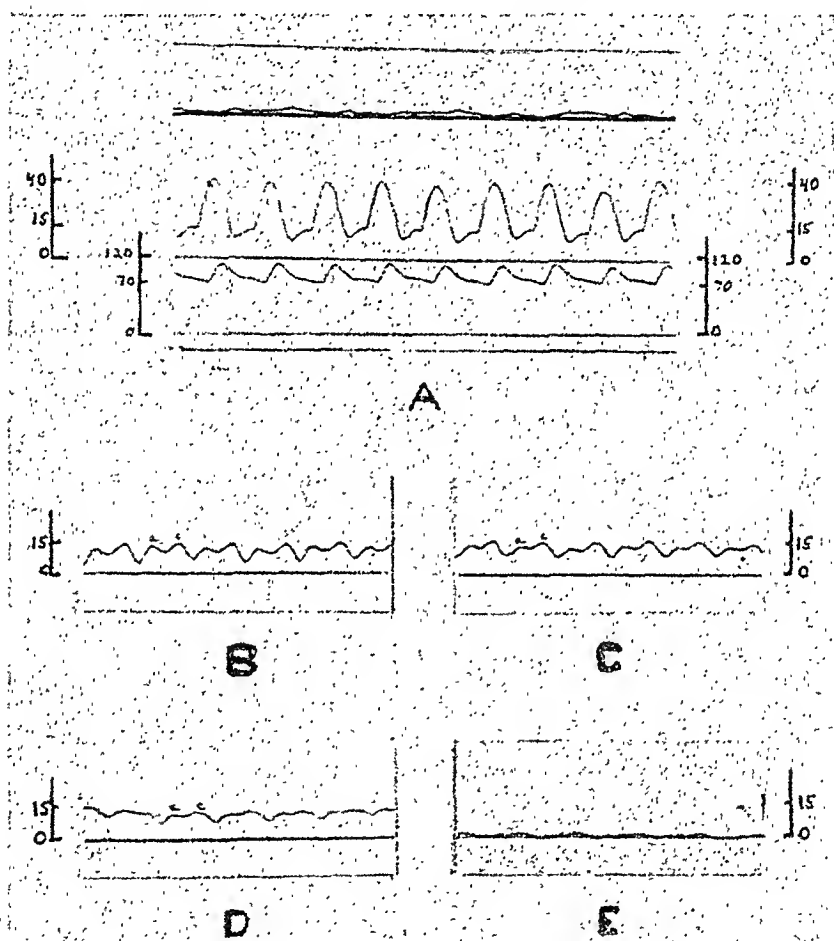


Fig. 3.—A, Simultaneous right ventricular and femoral pressure curves, taken with the catheter in the position shown in Fig. 2. B, Auricular pressure curve at the tricuspid valve. C, Auricular pressure curve taken at the level of the second anterior intercostal space. D, Pressure curve taken in the brachial vein. E, Pressure curve taken in external jugular vein two weeks later.

The pressure tracings at this point were identical with the previous ones (Fig. 3, A). Upon withdrawing the catheter from the right ventricle while taking a continuous pressure tracing, a blood sample was taken close to the tricuspid valve, where the pressure curve first changed from the ventricular to the auricular pattern. The respiratory gas content of this sample closely checked with the second ventricular sample (a carbon dioxide content of 51.2 volumes per cent and an oxygen content of 14.3 volumes per cent). The auricular

pressure tracings at this point showed evidence of tricuspid insufficiency, i.e., marked abnormal systolic increase in pressure. Unfortunately, these tracings were not timed by either an electrocardiogram or a femoral tracing (Fig. 3, *B* and *C*). Two further auricular blood samples were taken from the right auricle at about the level of the fourth anterior rib and second anterior intercostal space. The pressure tracings at these points were similar to those obtained from the tricuspid area but the respiratory gas contents, which checked one another, disclosed considerably more carbon dioxide (52.4 volumes per cent) and less oxygen (10.4 volumes per cent) than the one taken at the tricuspid valve. Pressure tracings taken in the brachial vein continued to show retrograde pulsations associated with tricuspid insufficiency, although ten days later, following a 25-pound diuresis, no evidence of tricuspid insufficiency could be found on an external jugular tracing (Fig. 3, *D* and *E*).

Summary.—The practically identical respiratory gas contents of the arterial and right ventricular blood samples prove the presence of a ventricular septal defect. A functional tricuspid insufficiency and right ventricular hypertension were demonstrated by the pressure tracings, the former being substantiated by the arterial contamination of the auricular blood sample taken at the tricuspid valve. In view of the extensive tricuspid insufficiency, no estimation of the peripheral blood flow was possible. The diminution of the pressure gradient between the peripheral and central venous pressures was an additional reflection of the extensive cardio-circulatory failure.

CASE 2.—T. P., a 16-year-old Negro schoolboy complained of a painless gradual enlargement of his abdomen for six months prior to his admission to the hospital. He had continued to participate in his usual activities, including basketball, without discomfort. He denied dyspnea, orthopnea, cough, or chest pain. The past history was entirely negative except for pneumonia at 9 and gonorrhea at 14 years of age. On admission, he was observed to be a well-developed and well-nourished boy. He could lie flat without discomfort. The heart was slightly enlarged both to the right and to the left. No thrill was palpable. The heart sounds were of good quality; P_2 was loud and snapping. A short, high-pitched, systolic murmur was heard slightly above the apex but was not transmitted. The liver was palpable 4 fingerbreadths below the costal margin and was very slightly tender. The spleen was palpable 3 fingerbreadths below the left costal margin. Neither ascites nor peripheral edema was present. Clubbing of the fingers or cyanosis was not observed. The laboratory findings were essentially negative; the blood count, erythrocyte sedimentation rate, and serum proteins were normal. The electrocardiogram showed a right-axis deviation, and a P-R interval of 0.26 second. T_1 and T_2 were isoelectric, T_3 showed low voltage, and T_{aR} was large. X-ray (Fig. 4) and fluoroscopic examination revealed the heart to be slightly enlarged to the right and to the left, with enlargement of the right ventricle and pulmonary conus, and a small aorta. The pulsations were good, except along the upper right border. The left auricle was markedly enlarged, displacing the esophagus posteriorly. There was no hilar dance. The roentgenogram was normal; pulsations were observed in all the visualized portions of the heart. The venous pressure was 347 mm. of saline, the circulation time was 15 seconds, and the vital capacity was 3,500 cubic centimeters. The clinical opinion in this case was divided between an interauricular septal defect and a constrictive pericarditis.

Procedure.—The catheter was passed without difficulty into the right auricle. This chamber did not appear to be enlarged. Due to the suspicion that an interauricular septal defect might be present, blood samples were

taken from the superior vena cava, from the hepatic vein, and from the right auricle before the catheter was slipped into the right ventricle. This chamber was markedly dilated. Simultaneous right ventricular and femoral arterial blood samples were withdrawn during the collection of expired air. Although the patient was hyperventilating moderately, his pulse remained constant. Manometric tracings were taken of the right ventricular, and, upon withdrawal, of the auricular pressures. A final auricular blood sample was withdrawn two and one-half hours after the first sample. The catheter was within the heart two hours and fifty minutes.

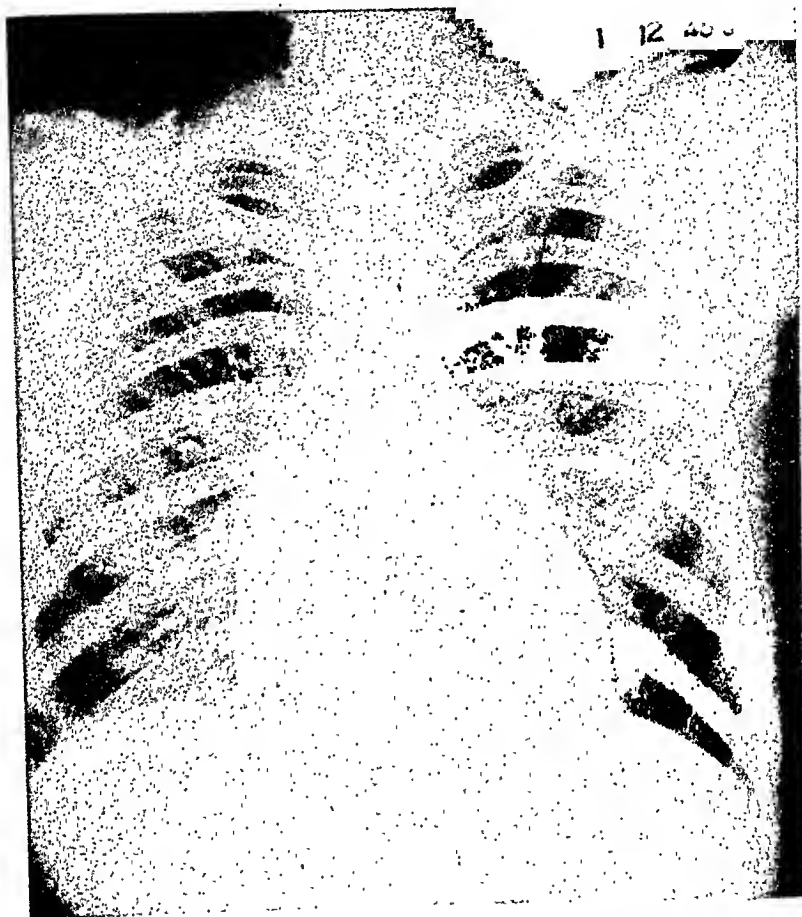


Fig. 4.—Roentgenogram of the thorax in Case 2; T. P.

The respiratory gas contents of the various blood samples and the times and location of sampling are presented in Table III. As can be seen, the gas contents of the hepatic vein and right auricular blood checked very closely even over a period of more than two hours, whereas the blood from the superior vena cava disclosed considerably more carbon dioxide and less oxygen. A difference of this magnitude between the gas contents of the superior vena caval blood and the right auricular and hepatic blood has not infrequently been observed. The presence of a small interauricular septal defect with the stream of blood flowing down into the tricuspid and hepatic vein region might be suspected on this data alone but would appear to be unlikely in the presence of a normal-sized auricle and a normal auricular pressure tracing. The ventricular blood, however, showed a marked degree of arterialization, which is consistent with the diagnosis

TABLE III. BLOOD GAS MEASUREMENTS

(T. P. [Case 2], male, 16 years old, oxyhemoglobin capacity 16.8 volumes per cent)

TIME	LOCATION OF CATHETER TIP	CARBON DIOXIDE CONTENT (VOLS. %)	OXYHEMO-GLOBIN CONTENT (VOLS. %)	PRESSURE (MM. HG)	OXYHEMO-GLOBIN SATURATION (%)
9:40 A.M.	Superior vena cava	43.1	9.0	mean 22	53.6
9:45 A.M.	Hepatic vein	41.5	10.9	--	64.9
9:50 A.M.	Right auricle	41.2	10.6	mean 22	63.1
10:58 A.M.	Right ventricle	38.8	13.9	54/25	82.8
10:58 A.M.	Femoral cannula	38.1	16.6	118/70	98.8
12:30 P.M.	Right auricle	40.9	11.0	mean 22	65.5

TABLE IV. HEMODYNAMIC MEASUREMENTS

(T. P. [Case 2], 16 years old; body surface area 1.87 M.²)

MEASUREMENTS	CONTROL	OBSERVED
Ventilation L./min./M. ² B. S. A.	4.04 ± 0.64	5.66
Pulse	66 ± 7.6	86
Oxygen consumption c.c./min./M. ² B. S. A.		129
Arteriovenous difference vol. %	4.5 ± 0.7	5.7
Systemic blood flow L./min./M. ² B. S. A.	3.12 ± 0.4	2.26
Plasma volume c.c./M. ² B. S. A.	1,600	2,370

TABLE V. BLOOD PRESSURE MEASUREMENTS

(T. P. [Case 2], pressure recorded in millimeters of mercury)

PRESSURES	FEMORAL ARTERY	RIGHT VENTRICLE	RIGHT AURICLE	PERIPHERAL VEIN
Systolic	118	54-47	27-25	
Diastolic	70	25-20	22-20	
Mean	80		22	22
Pulse	48	29-27		

of a left-to-right arteriovenous shunt and is associated with a marked dilatation of the chamber of the right ventricle. The pressure tracings showed a high ventricular systolic and diastolic pressure (Table V). Since the auricular tracing disclosed no evidence of a tricuspid insufficiency or patent auricular septum, it was possible to calculate the peripheral blood flow from the mean auricular and femoral blood oxygen difference (Table IV). That the patient was in a very steady state is indicated by a constant pulse and the close checks of the carbon dioxide contents of his auricular blood samples over a period of two and one-half hours. The hyperventilation observed during the collection of his expired air was apparent several days later when some respiratory studies were done under truly basal conditions, and thus it presumably was not induced by the procedure. His peripheral blood flow was low and there was a loss of pressure gradient between the peripheral and central veins, which findings confirmed the clinical impression of cardio-circulatory failure. Following these observations, the patient was digitalized, with a resulting weight loss of 11 pounds. Seven months later he re-entered the hospital in severe congestive failure with ascites and marked pitting edema which was improved by bed rest and diuresis.

Summary.—The arterialization of the right ventricular blood demonstrated the presence of an interventricular septal defect. The identical respiratory

gas contents of the hepatic vein and the auricular blood, and the absence of an enlarged right auricle practically rule out a functional auricular septal defect. The patient's congestive failure was reflected by a low peripheral blood flow, increased intraventricular and auricular pressures, a loss of pressure gradient between the peripheral and central veins, and an increased plasma volume.

DISCUSSION

The marked arterialization of the right ventricular blood of these two subjects is positive evidence of the presence of an arteriovenous shunt through the ventricular septum. Whether or not this defect is the only anomaly present in these patients cannot be stated. In the absence of infection, congestive failure in pure ventricular septal defect is considered unusual. Of Abbott's 50 "pure" cases, only four died of cardiac insufficiency. In the autopsy files of the Presbyterian Hospital, six cases are listed as having an isolated ventricular septal defect, in two of which the cause of death was cardiac insufficiency. It is obvious that the septal defect was large in both of our patients. Although in the case of A. S. (Case 1) the first ventricular sample must have been taken directly from the arterial stream, the second ventricular and first auricular samples are probably more representative of the mean ventricular mixture, of which approximately 70 per cent must have come from the arterial side. Similarly, the percentage of arterial blood in the ventricular sample taken from T. P. (Case 2) must have been in the neighborhood of 60. It therefore seems logical to conclude that the apparent large size of the arteriovenous shunt contributed materially to the development of cardio-circulatory failure in these two subjects. Moreover, in our first case there was some questions of a pericarditis being present, based upon poor pulsations of the right heart border and calcification in the region of the right ventricle. Dr. Robert Levy considered the possibility of an additional patent ductus arteriosus as contributing to heart failure. It is of interest that in both these patients congestive failure became crippling at the ages of 15 and 16 years, respectively, in view of the fact that Abbott's figures indicate that the average life expectancy of individuals with a ventricular septal defect is 14½ years.

Upon routine x-ray and fluoroscopic examination, the esophagus of each of these patients was considered to be displaced posteriorly by what was interpreted as an enlarged left auricle, but with the catheter in place it appeared to be the right ventricle. In the first case the catheter tip was observed to be closely adjacent to the vertebral column in one position, as well as beneath the sternum anteriorly in another (Fig. 2). Thus, in this subject the right ventricle appeared to fill almost the entire anterior posterior plane of the thoracic cage. In the second patient an attempt was made to pass the catheter into the pulmonary artery. During this unsuccessful attempt the catheter tip was seen to move along within the prominence which formed the left upper heart border, identifying this to be part of the enlarged right ventricle. These observations emphasize the difficulties of an attempted interpretation of the homogenous cardiac shadow without the aid of a contrast medium.

The detection of an arteriovenous shunt by this method is obviously dependent upon having a sufficiently large admixture of arterial blood bathing the tip of the catheter during the collection of the sample to produce a significant auricular ventricular oxygen difference. Obviously many smaller shunts can be missed by this method. Since the usual anatomic site for these defects is at the base of the heart, the tip of the catheter should be directed to that location for at least one sampling. In smaller septal defects the additional findings of right ventricular dilatation and/or hypertension would not be anticipated. But if a bacterial implantation were present, a positive blood culture might be obtained.

SUMMARY

Observations made by means of right heart catheterization upon the hemodynamics of two subjects with congestive failure of obscure etiology are reported.

In both subjects a large ventricular septal defect was demonstrated by the arterialization of the right ventricular blood.

The authors are greatly indebted to Dr. Dickinson W. Richards, Jr., and Dr. André Cournand for their advice and helpful criticism.

REFERENCES

1. Abbott, M. E.: *Congenital Heart Disease*. Nelson New Loose Leaf Medicine, New York, 1920, Thos. Nelson & Sons, vol. IV, pp. 207-321.
2. White, P. D.: *Heart Disease*, ed. 3, New York, 1944, The Macmillan Co., p. 296.
3. Cournand, A., Riley, R. S., Baldwin, E. deF., and Richards, D. W., Jr.: Measurement of Cardiac Output in Man, *J. Clin. Investigation* 24: 106, 1945.
4. Hamilton, W. F., Brewer, G., and Brotiman, I.: Pressure Pulse Contours in an Intact Animal. I. Analytical Description of a New High-Frequency Hypodermic Manometer With Illustrative Curves of Simultaneous Arterial and Intracardiac Pressures, *Am. J. Physiol.* 107: 427, 1934.
5. Peters, J. P., and Van Slyke, D. D.: *Quantitative Clinical Chemistry*, vol. II, Methods, Baltimore, 1931, Williams & Wilkins Co., p. 324.
6. a. Cournand, A., Lawson, H. D., Bloomfield, R. A., Breed, E. S., and Baldwin, E. deF.: Recording of Right Heart Pressures in Man, *Proc. Soc. Exper. Biol. & Med.* 55: 34, 1944.
b. Bloomfield, R. A., Lawson, H. D., Breed, E. S., and Cournand, A.: Measurements of Right Auricular and Ventricular Pressures and Description of Various Patterns of Intracardiac Tracings in Normal Man and Chest and Cardiovascular Disease. In press.
7. Stead, E. A., Jr., Warren, J. V., Merrill, A. J., and Brannon, E. S.: The Cardiac Output in Male Subjects as Measured by the Technique of Right Arterial Catheterization. Normal Values With Observations on the Effect of Anxiety and Tilting, *J. Clin. Investigation* 24: 326, 1945.
8. Cournand, A., Riley, R. L., Bradley, S. E., Breed, E. S., Noble, R. P., Lawson, H. D., Gregerson, M. I., and Richards, D. W., Jr.: Studies of the Circulation in Clinical Shock, *Surgery* 13: 964, 1943.
9. McMichael, J., and Sharpey-Schafer, E. P.: Action of Intravenous Digoxin in Man, *Quart. J. Med.* 13: 123, 1944.
10. Brannon, E. S., Merrill, A. J., Warren, J. V., and Stead, E. A., Jr.: The Cardiac Output in Patients With Chronic Anemia as Measured by the Technique of Right Arterial Catheterization, *J. Clin. Investigation* 24: 332, 1945.
11. Sharpey-Schafer, E. P.: Cardiac Output in Severe Anemia, *Clin. Sc.* 5: 125, 1944.

A SIMPLIFIED AND MORE STANDARDIZED TECHNIQUE FOR RECORDING MULTIPLE PRECORDIAL ELECTROCARDIOGRAMS

ARTHUR J. GEIGER, M.D., AND JESSAMINE R. GOERNER, M.D.
NEW HAVEN, CONN.

ALTHOUGH the superiority of multiple chest leads to any single precordial placement is well known to electrocardiographers, the majority of laboratories and physicians still fail to take advantage of this fact in routine electrocardiography. It is probable that this dilatoriness in adopting a technique of proved value is attributable to several factors: (1) the recording of multiple chest leads instead of a single one calls for additional technical time and effort, (2) the average laboratory technician is probably incapable of selecting correctly the anatomic sites specified by the American Heart Association for the six precordial placements,¹ and (3) there is still uncertainty and inadequate information concerning the normal criteria for chest lead electrocardiograms obtained from all six precordial placements with the four conventional attachments of the indifferent or distant electrode. This last deficiency would undoubtedly be remedied sooner if the retarding influence of the first two factors named were removed, and then the routine employment of multiple precordial derivations would probably be more widely adopted.

In an effort to expedite, simplify, and expand the practice of recording multiple precordial lead electrocardiograms, we have devised and studied the procedure described in this paper. Ample preliminary tests appear to establish the procedure as clinically useful and reliable.

METHODS AND PROCEDURE

Instead of identifying each of the precordial lead placements individually as recommended by the American Heart Association, the technique we employed requires finding only Positions 1 and 6, both easily identified; Positions 2 through 5 fall arbitrarily at even distances between 1 and 6. This is accomplished by the use of an elastic electrode belt made of good quality rubber of uniform elasticity. The belt, which is 3 cm. wide and at least 120 cm. long, is perforated at intervals of 4 cm. with holes sufficiently large to hold the handles of the six chest electrodes.* After the patient's chest has been marked in Position 1 (right sternal margin at fourth intercostal space) and Position 6 (midaxillary line halfway between the axilla and the costal margin†), the belt is applied

From the Department of Internal Medicine, Yale University School of Medicine, New Haven, Conn.

Received for publication Nov. 23, 1945.

*Belt and circular electrodes (3 cm. in diameter) supplied by Cambridge Instrument Company, New York, N. Y.

†This point falls within ± 1 cm. of the midaxillary point reached by "a line drawn from the left sternal margin in the 4th intercostal space to the outer border of the apex beat (or to a point of junction of the midclavicular line and the 5th intercostal space) and continued around the left side of the chest," as specified by the American Heart Association.²

so that the first electrode overlies Position 1 and the sixth electrode overlies Position 6; the four intermediate electrodes will then lie at even distances between the first and sixth as determined by the stretch of the belt. Electrode jelly is applied to the surface of each electrode by lifting one edge, and satisfactory contact is obtained by twirling the electrode against the skin. In recording the six chest leads the precordial lead wire is connected with each of the electrodes in turn, or a six-station switching device* may be interposed. Fig. 1 illustrates the electrode belt and switch.

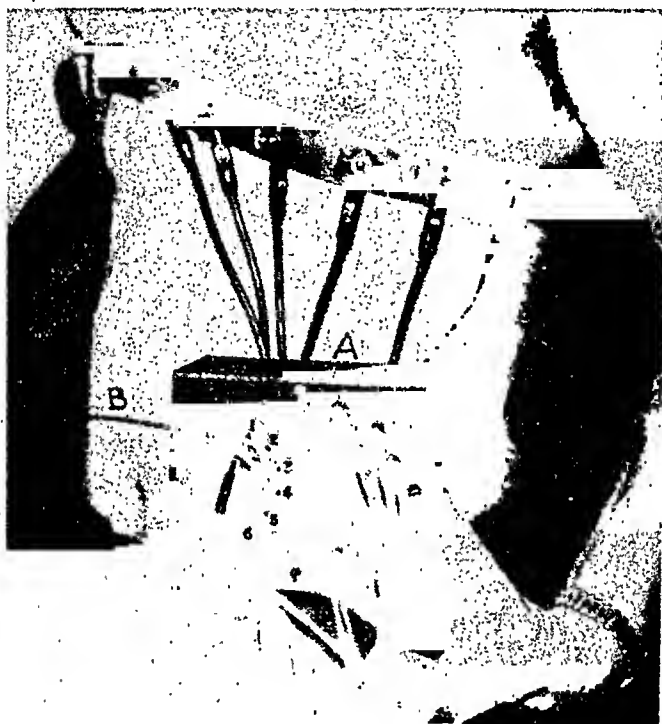


Fig. 1.—Left oblique view of the electrode belt in use. The switchbox, A, is an optional convenience for rapid recording from each of the six precordial positions; if the switchbox is not used, the chest lead wire, B, from the electrocardiograph is simply connected in succession with each of the six precordial electrodes.

Whether one follows the precordial placements recommended by the American Heart Association or utilizes the belt technique described, Positions 1 and 6 will be identical, but Positions 2 through 5 may differ moderately between the definitive official placements and the more arbitrary placements imposed by the belt. Fig. 2 illustrates the differences in the electrode positions of the two techniques on the thorax of a man of intermediate size and build.

The validity of the belt technique may be assessed, in part, by noting how closely the electrocardiograms obtained by the belt placements of the electrodes resemble the tracings obtained by the definitive anatomic placements. Such a study was undertaken on normal subjects and on a group of patients with cardiac and electrocardiographic abnormalities. The normal group included subjects of both sexes and of all body types from the asthenic, whose vertical hearts were

*Obtained from Sanborn Company, Cambridge, Mass.

largely retrosternal, to the extremely obese and hypersthenic with relatively horizontal position of the heart. All electrocardiograms were obtained with the subject reclining and with the trunk elevated to an angle of 45 degrees. The six precordial electrocardiograms were recorded by both the conventional and the belt techniques, with the indifferent electrode attached successively to the right arm, left arm, left leg, and to a central terminal of 5,000 ohms resistance.* The galvanometer was adjusted to a sensitivity of 1 cm. per millivolt. The two series of twenty-four electrocardiograms each, obtained by the two techniques, were then carefully compared.

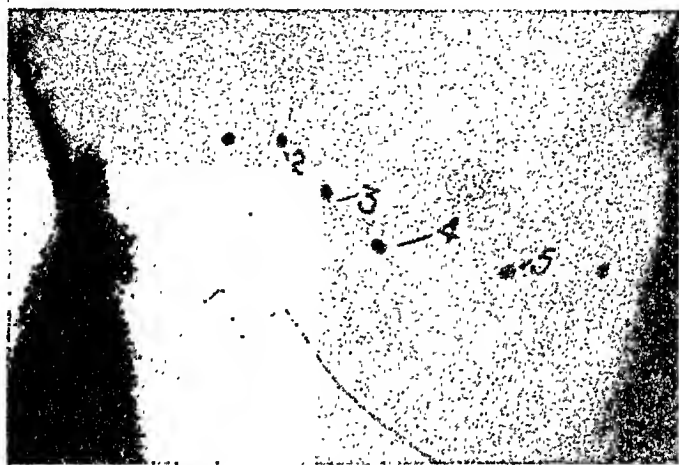


Fig. 2.—The blackened circles mark the six precordial electrode positions as defined by the American Heart Association; the numerals indicate the positions assumed by the electrodes with the elastic belt technique. The subject was a man of intermediate build whose electrocardiograms obtained by the two techniques are compared in Experiment 1 of Table I.

RESULTS

I. *Normal Subjects.*—Thirty normal young adults (fifteen men and fifteen women) were selected as experimental subjects. Two parallel series of chest lead electrocardiograms were made upon each by the conventional and the belt techniques described; the results were carefully compared and the differences were tabulated.

Auricular deflections are usually poorly represented in precordial leads as compared with limb leads; the slight differences that occurred occasionally in P waves of the two series were considered insignificant. For the purposes of this study attention was focused on the details of the ventricular complexes. The dissimilarities noted are summarized for the male and female subjects in Tables I and II; where differences existed the actual amplitudes of the deflections are stated in millimeters, with the value by the conventional technique to the left of the colon (:) and the value by the belt technique to the right.

It may be seen from the tabulations that only exceedingly slight or imperceptible differences were noted between the twenty-four pairs of tracings in eleven of the subjects (*Grade of Similarity: A*). Figs. 3A and 3B illustrate the remarkable similarity of the comparable electrocardiograms in a representative subject of this group.

*These four peripheral attachments were easily and quickly made through the use of a suitably designed switching device made for us by Sanborn Company, Cambridge, Mass.

In sixteen cases there were moderate differences, usually in the relative amplitudes of R and S, and occasionally in the amplitude of T (*Grade of Similarity: B*). Figs. 4A and 4B illustrate the tracings in a typical case of this group.

In three cases the records were classified *Grade of Similarity: C*, because either Q or S was present in some of the tracings by one technique and absent by the other, or because T was oppositely directed in one or more tracings of the two parallel series. Inspection of the data in Tables I and II will reveal

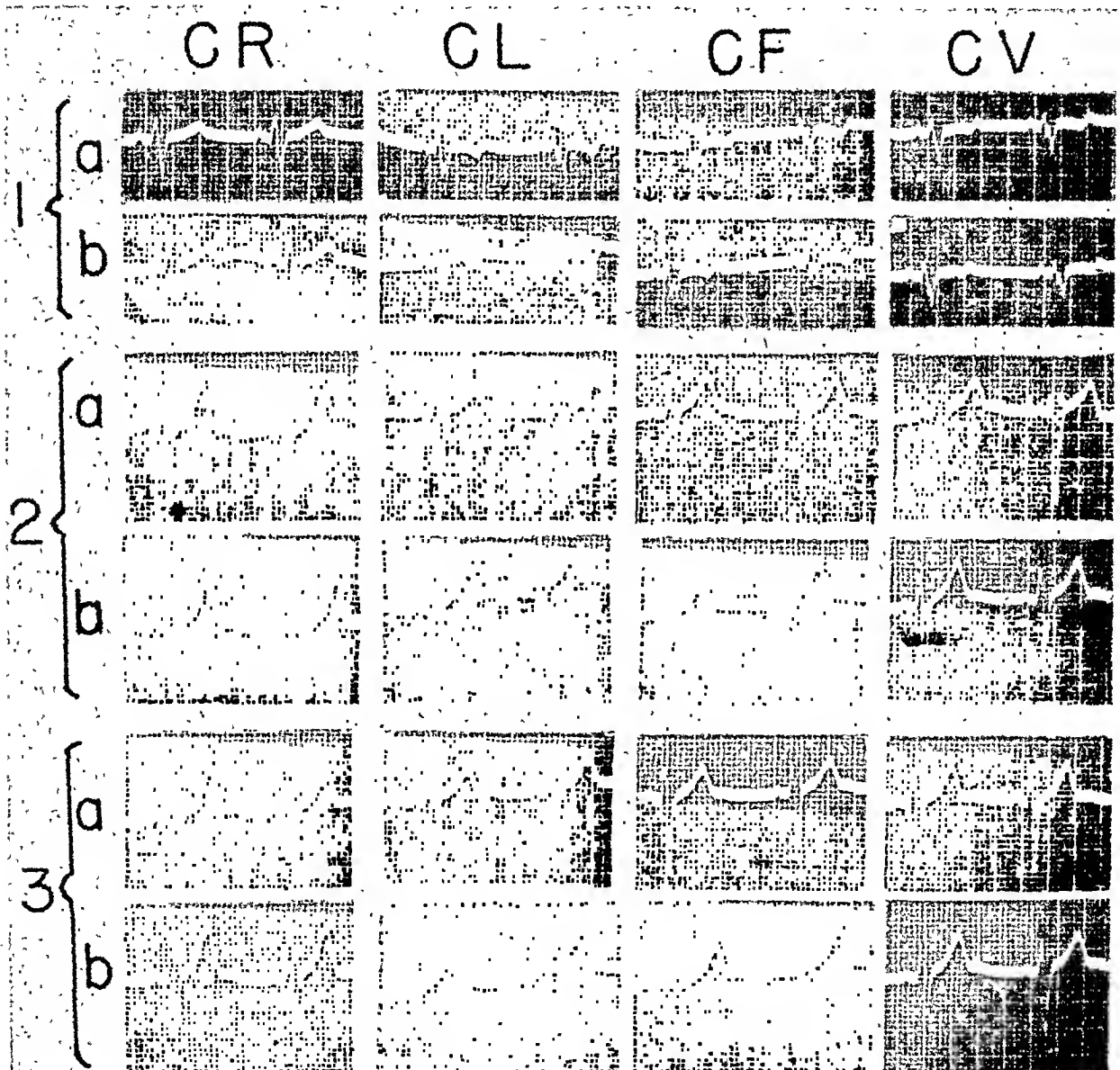


Fig. 3A.

Figs. 3A and 3B.—Normal male subject (N. J.). In this and the figures that follow, CR, CL, CF, and CV refer to the placements of the indifferent (distant) electrode on the right arm, left arm, left leg, and a central terminal of 5,000 ohms resistance, respectively. The arabic numerals 1 to 6 refer to the precordial positions of the exploring (near) electrode; the suffixes a and b indicate electrocardiograms obtained by the conventional and belt techniques, respectively (see text for details).

that Q-, S-, and T-wave differences in this group concerned only deflections of very small amplitude. Figs. 5A and 5B illustrate the electrocardiographic differences in one of these three most dissimilar cases.

The QRS patterns were slightly more variable in the female series than in the male, yet without apparent correlation with body build. Also, several of the women consistently yielded tracings with more or less serious artifact in the

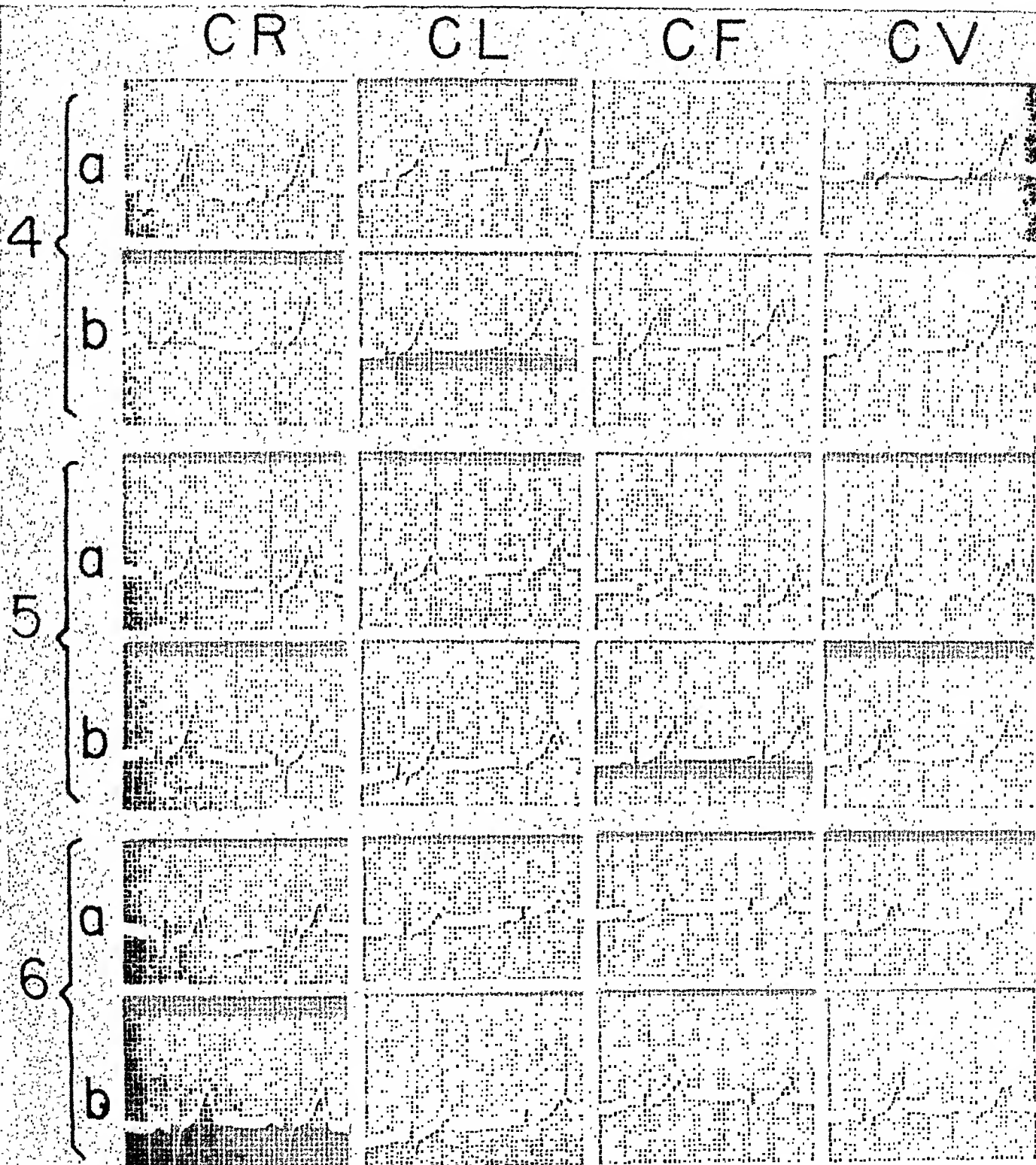


Fig. 3B.—(For legend see Fig. 3A.)

form of baseline movement, especially in Positions 4, 5, and 6 with the belt technique. This artifact was proved not to be due to muscle tremor; it seemed related to the use of smooth-surfaced electrodes in the three lateral positions. By substituting grooved electrodes in these positions the artifact was eliminated;

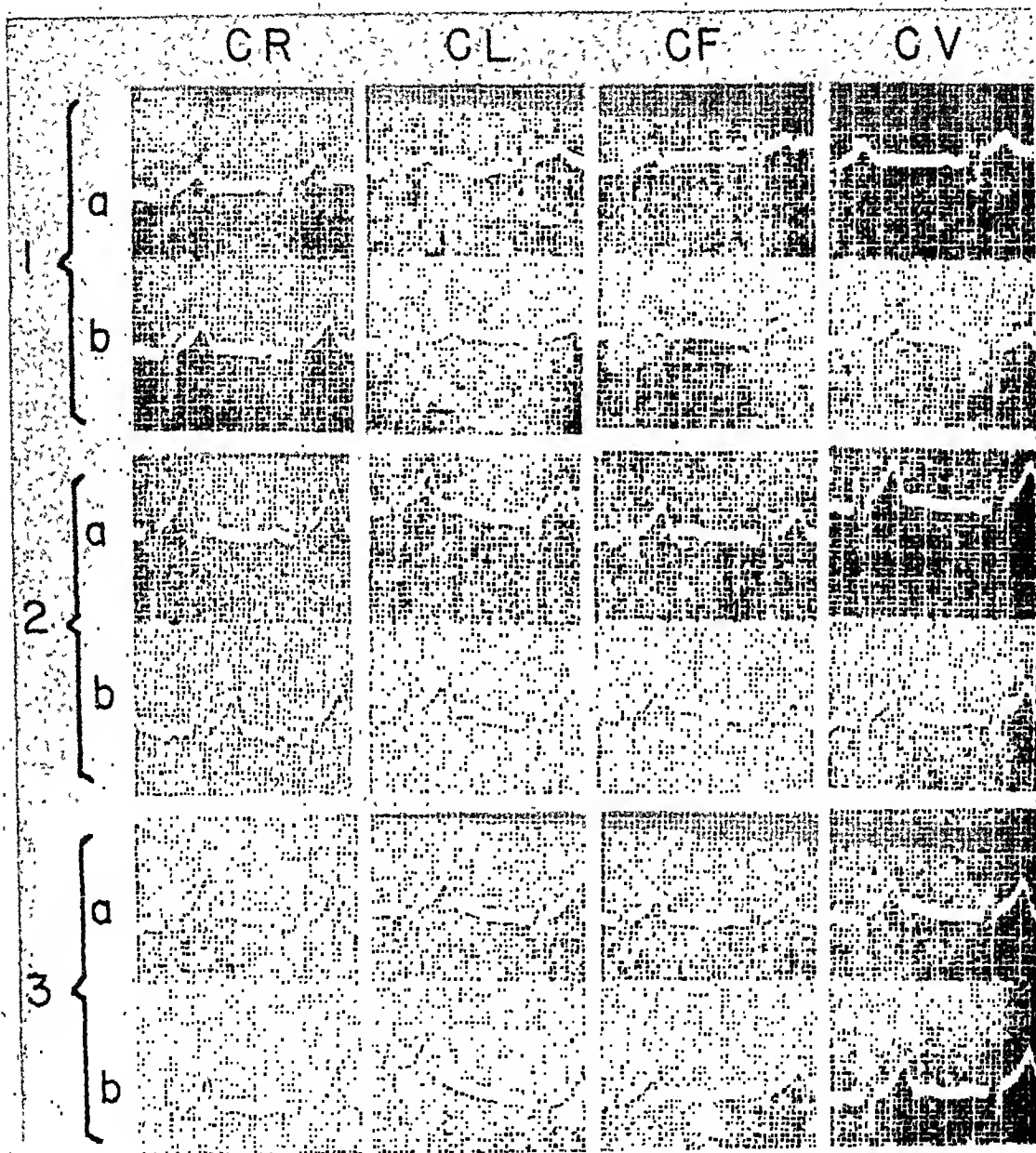


Fig. 4A.

Figs. 4A and 4B.—Normal male subject (H. H.).

this suggested that imperceptible slipping of the electrodes in the region of the female breast was the cause of the difficulty.

It was interesting to observe that relative largeness of deflections in comparable tracings was not a uniform characteristic of either technique. Thus, as may be seen in Tables I and II, a given deflection was sometimes of greater

amplitude with one technique than with the other in a given subject, while in another subject the same technique yielded relatively smaller deflections; and in some instances relative largeness of given deflections was manifested alternately by the two techniques, not only between different electrode positions but also with the same position on changing from one to another of the four indifferent peripheral electrode attachments.

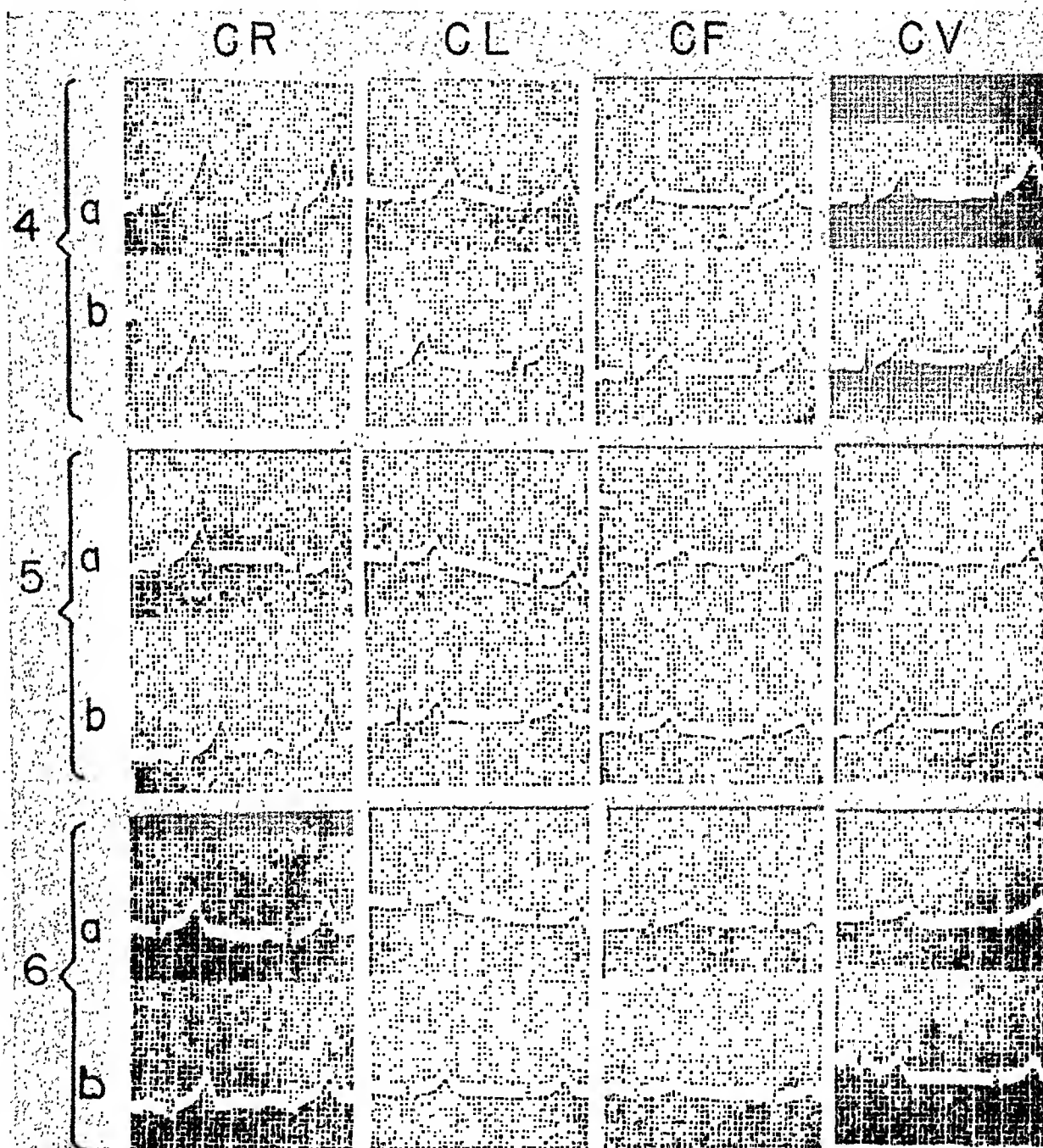


Fig. 4B.—(For legend see Fig. 4A.)

It is apparent from the representative illustrations and from the details given in Tables I and II on all thirty normal subjects that in no case were the differences between the electrocardiograms obtained by the two techniques of such nature or degree as to be clinically significant.

That the recorded dissimilarities, though relatively minor, were not necessarily attributable to positional variations of the chest electrodes between the conventional and the belt placements was suggested by the observation that even the tracings obtained from the first and from the sixth positions, whose placements were identical in the two techniques, showed occasional differences.

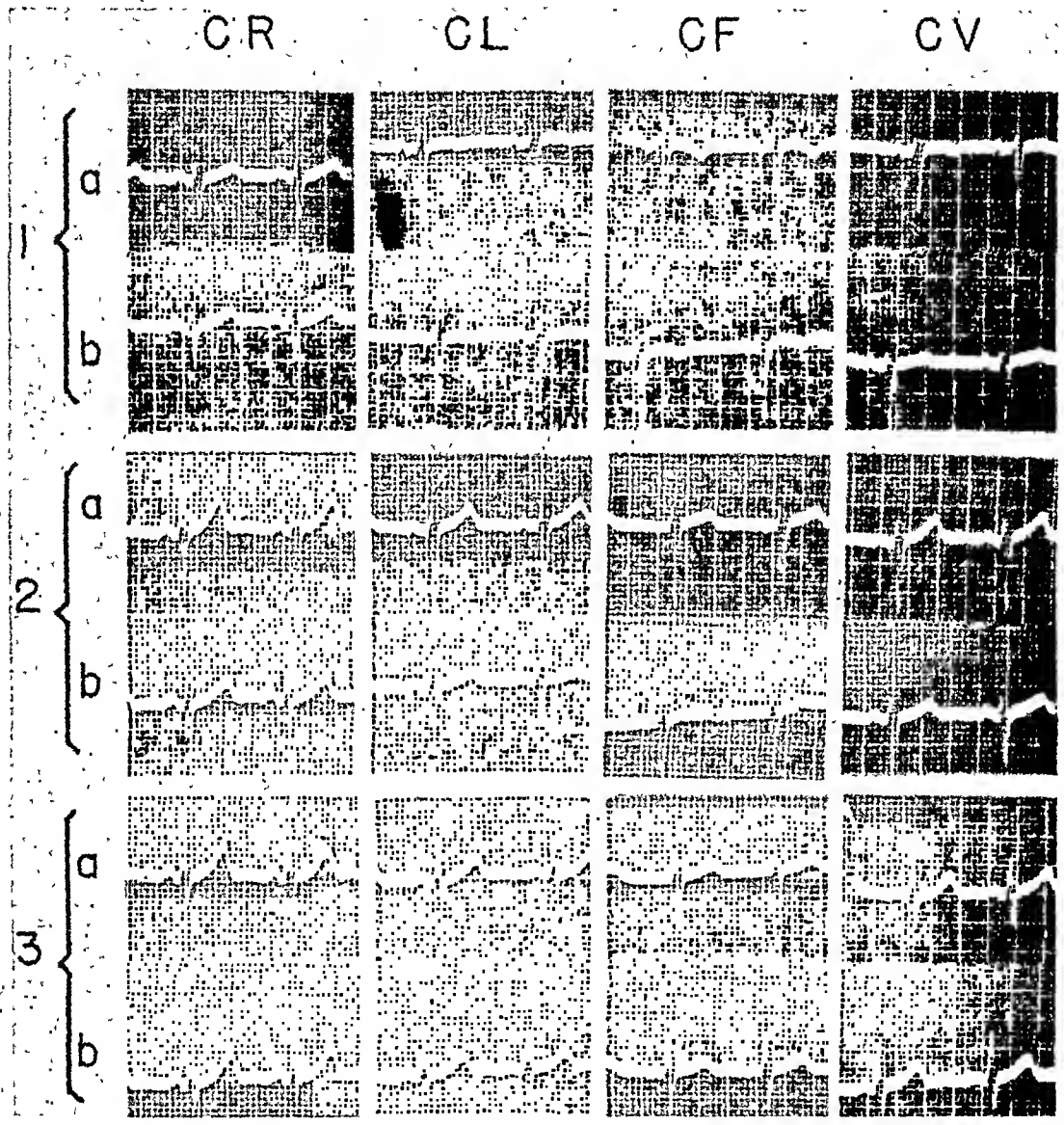


Fig. 5A.

Figs. 5A and 5B.—Normal female subject (R. W.).

This clue was pursued further by the repeated recording of the twenty-four precordial tracings on twenty separate occasions in the same subject. The results are summarized in Tables III and IV, which reveal several facts of interest: (1) the series pairs were remarkably similar on some occasions, while at other times there were deviations in Q, R, S, and T which were quite equal to the differences noted among the thirty different subjects (compare Table III with

Tables I and II); (2) the grades of difference between the members of a pair of tracings *obtained by the two techniques* on any of the normal group were no greater than the variations noted in the series of twenty records on the same subject *employing the conventional technique alone* (compare Table IV A with Tables I and II); (3) there was actually greater uniformity in the series of twenty electrocardiograms obtained on the same subject by the belt technique than by the conventional selective placement of the chest electrode (Table IV B).

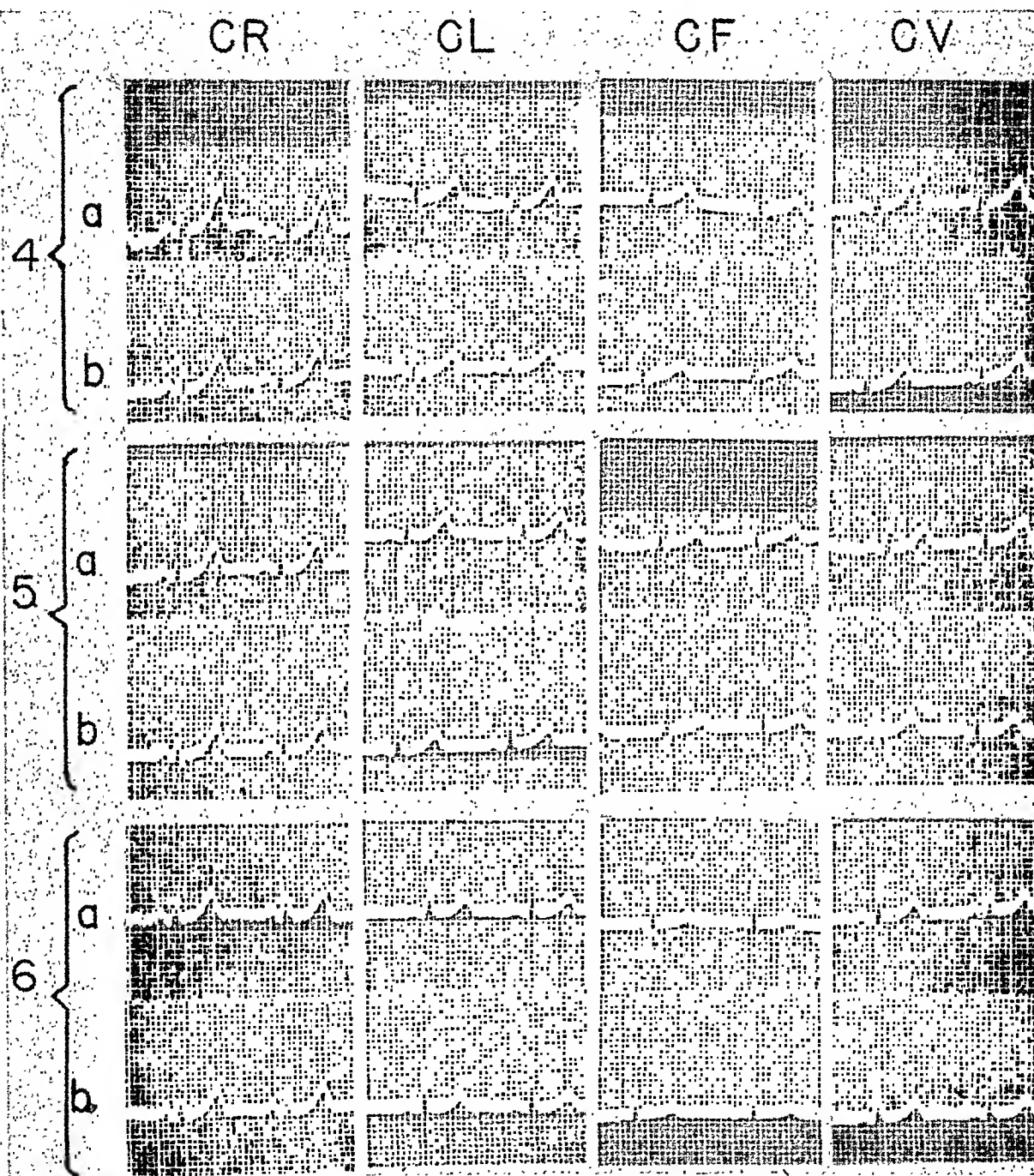


Fig. 5B.—(For legend see Fig. 5A.)

These observations indicate that most of the differences between the tracings obtained by the two techniques were probably of physiologic rather than technical origin. Variations in the height of the diaphragm, with resultant altera-

TABLE I. DIFFERENCES BETWEEN PRECORDIAL ELECTROCARDIOGRAMS OBTAINED BY CONVENTIONAL AND BELT TECHNIQUES IN FIFTEEN NORMAL MALE SUBJECTS

(Amplitudes of deflections with conventional and belt techniques appear to left and right of colon, respectively.)

NO.	SUBJECT	LEAD POSITION	LEAD CR			LEAD CL			LEAD CF			LEAD CV			GRADE*
			R	S	T	R	S	T	R	S	T	R	S	T	
1	A. G. (intermediate)	1, 2, 3, 6 4 5	No differences between conventional and belt series in these leads												
			0	0	0	0	4:5	0	0	3:4	0	0	0	0	
			0	1:2	0	0	0	0	0	1/4:1/2	0	0	0	0	A
2	N. J. (hypersthenic)	1-6	No differences												A
3	N. T. (hypersthenic)	1-6	No differences												A
4	H. L. (sthenic)	1, 4 2 3 5 6	No differences												B
			0	0	0	0	18:14	0	0	15:11	0	0	16:11	0	
			0	9:8	0	0	9:8	0	0	7:5	0	0	0	0	
			0	0	0	10:15	0	0	0	0	0	15:17	0	0	
			14:17	0	0	5:9	0	0	7:10	0	0	8:11	0	0	
5	R. J.	1, 3, 4, 5, 6 2	No differences												A
			0	0	0	0	0	0	0	17:12	0	0	14:10	0	
6	H. D. (intermediate)	1, 6 2 3 4 5	No differences												A
			0	0	0	5:6	12:10	0	0	18:14	0	0	15:11	6:5	
			0	0	0	0	13:10	0	0	0	0	0	0	0	
			21:15	7:8	0	15:10	6:8	0	13:8	0	0	17:10	6:8	0	
			0	2:4	0	0	2:3	0	0	2:5	0	0	2:4	0	
7	M. B. (intermediate)	1, 2, 3, 5, 6 4	No differences												A
			7:5	8:9	0	4:3	0	0	4:3	0	0	4:3	0	0	
8	J. K. (sthenic)	1, 6 2 3 4 5	No differences												B
			0	10:7	0	0	13:6	0	0	17:8	0	0	13:6	0	
			7:12	7:5	0	4:7	5:4	0	3:7	7:5	0	0	6:8	0	
			20:15	0	0	23:10	0	0	19:11	2:4	0	23:14	2:3	0	
			0	0	0	0	0	0	0	0	0	0	0	0	

*Refers to degree of similarity between comparable tracings obtained by the conventional and precordial belt techniques. Grade A = excellent similarity; Grade B = good similarity; Grade C = fair similarity.

9	H. H. (hypersthenic)	1, 5 2 3 4 6	No differences 0 13:8 0 0 0 3:5 0 0	5:3 17:7 5:9 0 15:11 0 9:12 0	0 0 0 0 0 0 0 0	0 25:11 0 0 10:7 3:5 7:9 0	0 0 0 0 0 0 0 0	0 16:9 0 0 0 2:4 0 0	B
10	R. H. (sthenic, thin)	2, 5, 6 1 3 4	No differences 0 0 0 15:9 10:13 10:6	0 0 0 14:7 8:12 9:5	0 0 0 0 0 0	0 19:16 0 20:12 0 13:10	0 0 0 0 0 0	0 0 0 17:10 0 9:7	B
11	G. C. (hypersthenic) Wt. = 330 lb. Chest circum. = 148 cm.	1 2 3 4 5 6	0 0 0 1:1½ 0 0 0 0 0 0 24:29 0	0 0 0 1½:1 0 0 16:13 0 0 0 10:15 0	0 1½:1 0 2:3 0 0 0 0	0 0 0 0 0 2½:3 0 1:2 0 0 15:20 0	0 0 0 0 0 0 0 0 0 0 0 0	0 0 0 0 0 0 0 0 0 1½:2 0 1:1½	B
12	F. B. (sthenic)	1 2 3 4 5 6	0 0 0 15:10 0 9:5 12:9 5:4 17:11 1:3 15:12 ¼:2	0 0 0 0 4:3 11:6 9:6 7:5 14:9 0 13:9 ¼:1	0 0 0 0 0 0 0 0 0 0	0 0 0 22:16 10:6 6:4 5:4 6:4 ¼:1 0 0 ¼	0 0 0 0 4:3 4:3 7:5 5:4 12:7 1:2 10:8 ¼:1	0 2:3 0 0 0 19:13 0 10:6 6:5 7:6 0 0	B
13	T. S. (intermediate)	1 2 3 4 5, 6	0 0 0 0 13:11 0 17:14 3:4 No differences	0 0 0 10:6 0 6:5 8:6 0	0 -½:±½ 0 0 0 0 0 0	0 6:3 0 5:2 0 3:2 0 0	0 0 0 0 0 0 0 0	0 6:5 0 7:4 0 4:3 0 0	B
14	D. S. (sthenic)	1-5 6	No differences 0 0	0 0	0 0	0 0	0 3:1	0 0	A
15	C. McL. (sthenic)	1 2 3 4 5 6	6:4 8:5 6:10 10:4 0 0 0 0 0 0 11:18 0	4:3 10:8 5:4 15:7 0 0 11:9 0 0 0 8:10 0	4:2 4:2 5:4 5:4 0 0 0 0 0 0 3:4 0	12:8 4:2 12:6 6:4 0 0 0 0 0 0 5:10 0	0 11:4 13:7 6:5 0 0 0 0 0 0 7:10 2:3 0 2:4	5:3 7:6 0 0 0 0 0 0 0 0 9:11 0 7:10 3:4	B

TABLE 11. DIFFERENCES BETWEEN PRECORDIAL ELECTROCARDIOGRAMS OBTAINED BY CONVENTIONAL AND BELT TECHNIQUES IN FIFTEEN NORMAL FEMALE SUBJECTS

(Amplitudes of deflections by conventional and the belt techniques appear to left and right of colon, respectively.)																							
No.	SUBJECT	LEAD POSITION	LEAD CR				LEAD CL				LEAD OF				LEAD CV				GRADE*				
			Q	R	S	T	Q	R	S	T	Q	R	S	T	Q	R	S	T					
1	D. P. (sthenic)	1, 2	No differences between conventional and belt series in these leads																A				
		3	0	0	5:4	0	0	0	0	8:4	0	0	0	0	0	0	0	0		7:4	0		
		4	0	0	0	0	4:8	0	0	0	0	4:7	0	0	0	0	0	8:10		0	0		
		5	0	0	0	0	6:8	0	0	0	0	4:7	0	0	0	0	0	7:9		0	0		
		6	0	12:15	0	0	7:9	0	0	0	0	5:7	0	0	0	0	0	0		0	0		
2	G. B. (sthenic, obese)	1, 5	No differences																A				
		2	0	9:11	7:3	0	0	0	0	7:4	0	0	0	0	0	0	0	12:10		3:2	0		
		3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0	0		
		4	0	21:18	0	0	0	0	0	13:12	0	0	0	0	0	0	0	0		0	0		
		6	0	13:16	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0	0		
3	L. W. (sthenic)	2, 3, 5	No differences ^a																B				
		1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0	0		
		4	0	11:13	0	0	0	0	0	7:9	0	0	0	0	0	0	0	8:10		0	0		
		6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0	0		
		No differences			0			-1:-1/2			0			0			0			0			
4	R. S. (intermediate)	1, 6	No differences																B				
		2	0	13:11	16:13	0	0	12:9	23:17	0	0	11:9	25:19	0	0	0	11:9	20:15		0	0		
		3	0	0	9:15	0	0	8:6	20:11	0	0	8:6	20:12	0	0	0	0	16:11		0	0		
		4	0	0	0	0	0	7:9	9:4	0	0	0	10:15	0	0	0	0	11:5		0	0		
		5	0	11:14	10:4	5:4	0	0	4:2	0	0	0	4:2	0	0	0	0	4:2		0	0		
		6	0	0	0	0	0	0:1/4	0	0	0	0	0	0	0	0	0	0		0	0		
5	S. P. (hypersthenic)	1, 4	No differences																B				
		2	0	0	8:4	0	0	2:6	2:0	0	0	2:5	4:2	0	0	0	3:10	2:1/4		0	0		
		3	0	11:16	2:3/4	0	0	0	0	0	0	9:7	0	0	0	0	14:11	0:3/4		0	0		
		5	0	19:16	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0	0		
		6	0	0	9:7	0	0	7:9	0	0	0	0	0	0	0	0	0	0		0	0		
6	J. M. (hypersthenic)	1, 3, 5, 6	No differences																C				
		2	0	0	9:6	6:3	0	0	0	10:8	4:2	0	0	0	0	0	0	0		0	5:3		
		4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0	6:5		
7	P. V. (intermediate)	1, 5	No differences																B				
		2	0	8:5	0	0	0	0	0	0	0	0	0	0	0	0	0	6:4		0	1 1/2:1/2		
		3	0	12:8	0	0	0	7:5	0	1 1/2:1	0	0	7:1	0	0	0	0	9:6		0	3:2		
		4	0	0	0	0	0	10:8	4:3	0	0	0	0	0	0	0	0	13:10		0	0		
		6	0	0	0	0	0	0	1/4:1 1/2	0	0	1:2	0	0	0	0	1/4:0	0		0			
8	M. F. (sthenic)	1, 6	No differences																B				
		2	0	6:3	0	0	4:2	4:7	5:3	0	0	0	0	0	0	0	0	4:2		5:8	0		
		3	0	7:5	0	0	0	4:2	0	0	0	0	0	0	0	0	0	0		0	0		
		4	0	0	0	0	0	17:14	0	6:4	0	0	10:8	0	0	0	0	0		0	0		
		5	0	0	0	0	0	18:15	0	4:3	0	0	0	0	0	0	18:15	0		0	5:4		

9	M. P. (intermediate)	I, 6	No differences	2:4	5:7	2:3½	0	2:5	0	1:3	0	0	12:10	½:2	0	2:4	0	1:3½	B
		2	0	0	8:6	0	0	0	8:5	0	0	0	11:6	0	0	0	9:6	0	
		3	0	0	0	0	0	15:18	0	7:4	0	9:4	0	6:4	0	11:7	0	7:6	
		4	0	18:10	0	0	0	16:13	0	0	0	12:9	0	4:3	0	16:11	0	5:4	
		5	0	18:16	0	6:5	0	0	0	0	0	0	0	0	0	0	0	0	
10	C. H.	1	0	7:6	9:6	2:1	0	6:5	18:16	0	0	6:5	16:14	0	0	6:5	0	½:1	B
		2	0	0	7:4	6:4	0	8:6	13:8	4:1½	0	9:7	12:9	4:2	0	9:7	10:7	5:2½	
		3	0	21:19	0	5:6	0	0	0	3:4	0	0	½:1	3:4	0	15:13	0	0	
		4	1:1½	0	0	0	0	0	0:½	3:4	0	0	0:½	3:4	0	0	0:½	3:¼	
		5	0	0	0	4:5	0:½	0	0	0	0	0	0	0	0	0	0	0	
		6	0	0	0	3:2	0	0	0	0	0	0	0	1:1½	1:½	0	0	0	
11	L. L. (sthenic)	1	0	0	7:6	-1:-½	0	4:3	9:7	0	0	0	0	0	0	0	8:7	0	B
		2	0	11:8	4:5	3:2	0	0	0	0	0	5:6	7:9	1:½	0	7:6	0	1:½	
		3	0	17:11	0	4:3½	0	12:9	3:4	0	0	8:6	3:4	2:1	0	12:9	3:4	3:2	
		4	0	19:17	0	0	0	16:13	0	4:3	0	0	0	4:3	0	16:14	0	0	
		5	0	0	0	5:4	0	0	0	0	0	0	0	0	0	0	0	4:3	
		6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
12	M. G. (sthenic)	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1:½	A
		2	0	0	8:9	0	0	0	8:7	1½:1	0	0	0	0	0	0	0	0	
		3	0	0	7:6	4:3	0	0	0	0	0	0	14:10	0	0	0	8:7	0	
		4	0	0	4:5	0	0	0	0	0	0	0	0	0	0	0	0	3:2	
		5	0	18:16	½:1½	5:7	0	0	0	3:4	0	7:6	0	0	0	14:8	½:1½	0	
		6	0	0	0	0	1:½	0	0	0	0	0	0	0	0	14:15	0	0	
13	R. W. (intermediate)	1	0	0	7:6	0	0	0	13:10	0	0	½:1	14:12	0	0	0	0	-½:½	C
		2	0	3:4	9:6	5:3	0	3:2	12:8	3:2	0	0	13:9	2:½	0	3:2	11:8	3:2	
		3	0	10:13	0	5:4	0	4:6	4:3	0	0	4:5	0	0	0	6:7	5:4	0	
		4	0	24:20	3:2	7:5	0	14:12	0	4:3	0	0	5:3	3:2	0	15:13	3:1	4:3	
		5	0	0	0	0	0	0	0	3:2	0	0	0	0	0	0	0	0	
		6	0:½	0	0	0	0	0	0	3:2	0	7:6	0	0	0	0	0	3:2	
14	S. K. (intermediate)	1	0	0	0	0:1	0	0	0	0	0	0	15:13	-4:-3	0	0	12:11	0	B
		2	0	0	15:13	4:3	0	3:2	22:19	1½:½	0	0	24:21	±2:±½	0	0	21:17	2:1	
		3	0	0	7:8	0	0	0	7:12	0	0	3:2	8:13	0	0	0	6:10	4:3	
		4	0	0	0	0	0	12:9	0	0	0	11:8	0	0	0	15:11	0	0	
		5	0	16:21	0	7:9	0	0	0	4:5	0	9:12	0	3:4	0	13:16	0	0	
		6	0	13:16	0	0	0	7:10	½:1	0	0	5:9	0	0	0	9:12	0	0	
15	J. McN. (hypersthenic)	1	0	0	7:5	0	0	4:3	11:8	0	0	0	16:13	0	0	0	10:9	0	C
		2	0	4:5	7:3	2:1	0	0	10:5	0	0	0	0	1½:1	0	0	10:4	0	
		3	0	8:13	0	0	0	4:8	3:2	0	0	0	0	0	0	4:8	3:1	1:1½	
		4	0:¼	16:18	0	3:2	0	10:13	0	0	0	5:7	2:1	2:1	0	11:12	1:½	1½:1	
		5	0	0	0	0	0	15:14	0	1:½	0	7:6	0	1:3	0	14:12	0	1:½	
		6	0	0	0	0	0	0	0	1:±½	0	4:5	0	0	1:½	0	0	1:½	

*Refers to degree of similarity between comparable tracings obtained by the conventional and precordial belt techniques. Grade A = excellent similarity; Grade B = good similarity; Grade C = fair similarity.

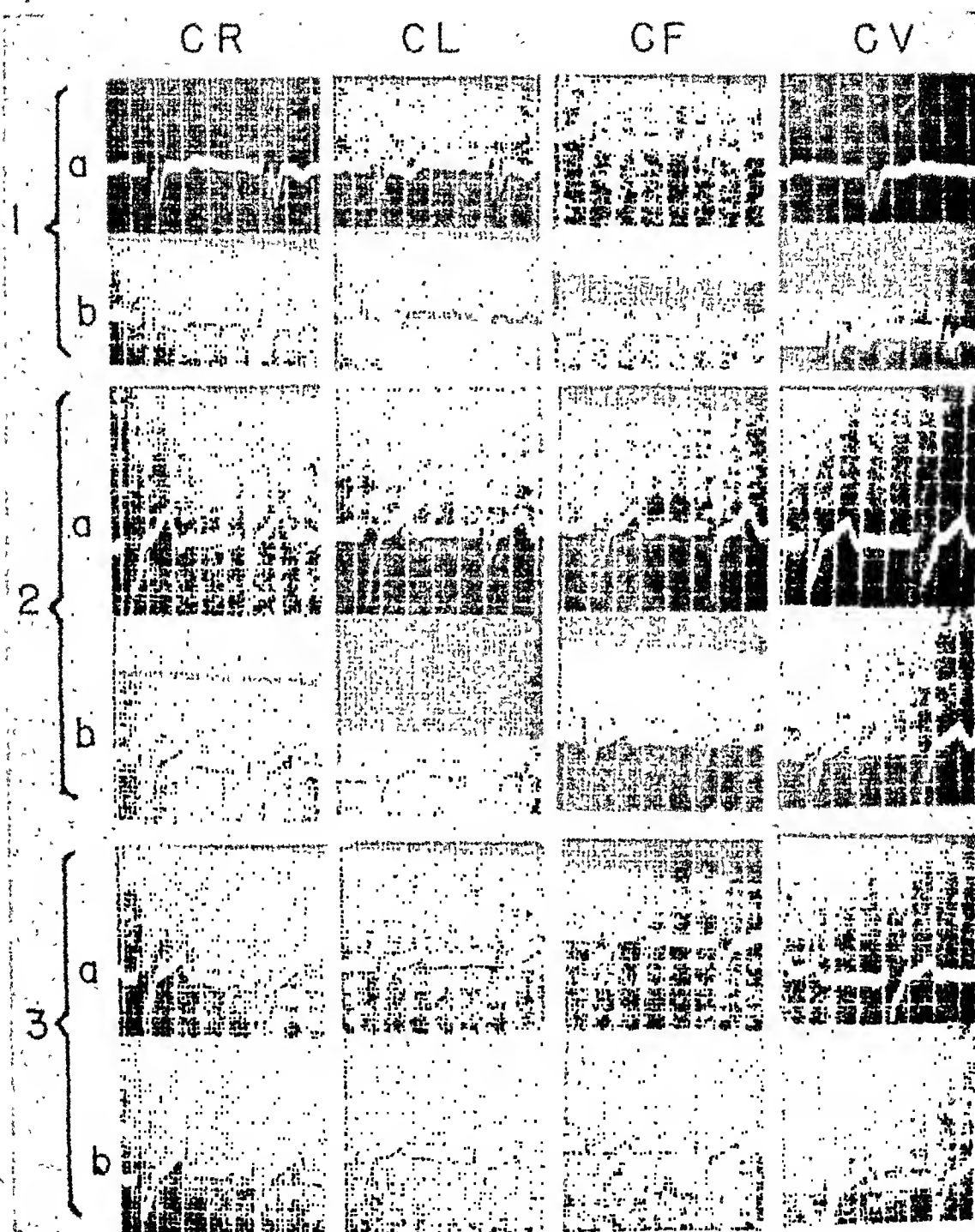


Fig. 6A.

Figs. 6A and 6B.—Patient L. G., whose limb lead electrocardiograms exhibited right bundle branch block.

tions in the position of the heart in relation to the overlying electrodes, probably explain many of the differences noted. Moreover, the belt technique seemed to permit more uniform reproduction of serial precordial electrocardiograms in the same subject from day to day.

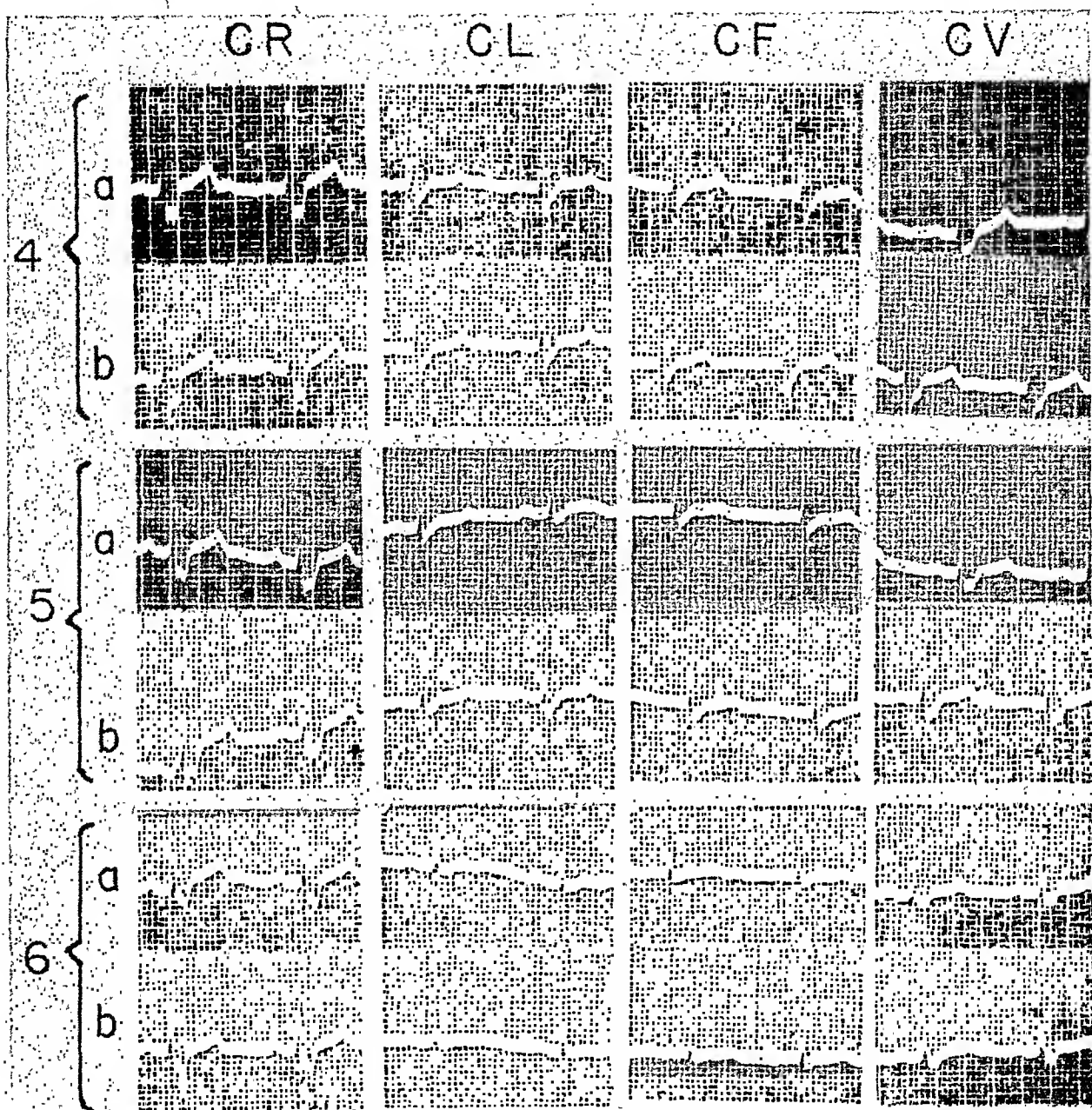


Fig. 6B.—(For legend see Fig. 6A.)

II. *Cardiac Cases.*—A small number of exploratory observations were carried out in patients with heart disease and abnormal electrocardiograms in order to observe again how closely the tracings obtained by the two techniques resembled each other. The cases selected were examples of those that exhibit gross and characteristic abnormalities of the QRS complex, RS-T segment, and T waves; they included examples of right and left bundle branch block, left ventricular hypertrophy and strain, and acute myocardial infarction. The re-

sults are best presented by the actual electrocardiograms obtained by each technique (Figs. 6 to 10).

As in the study of normal subjects, so in these pathologic cases, the differences in the tracings resulting from the two techniques were minor and, in our opinion, clinically insignificant.

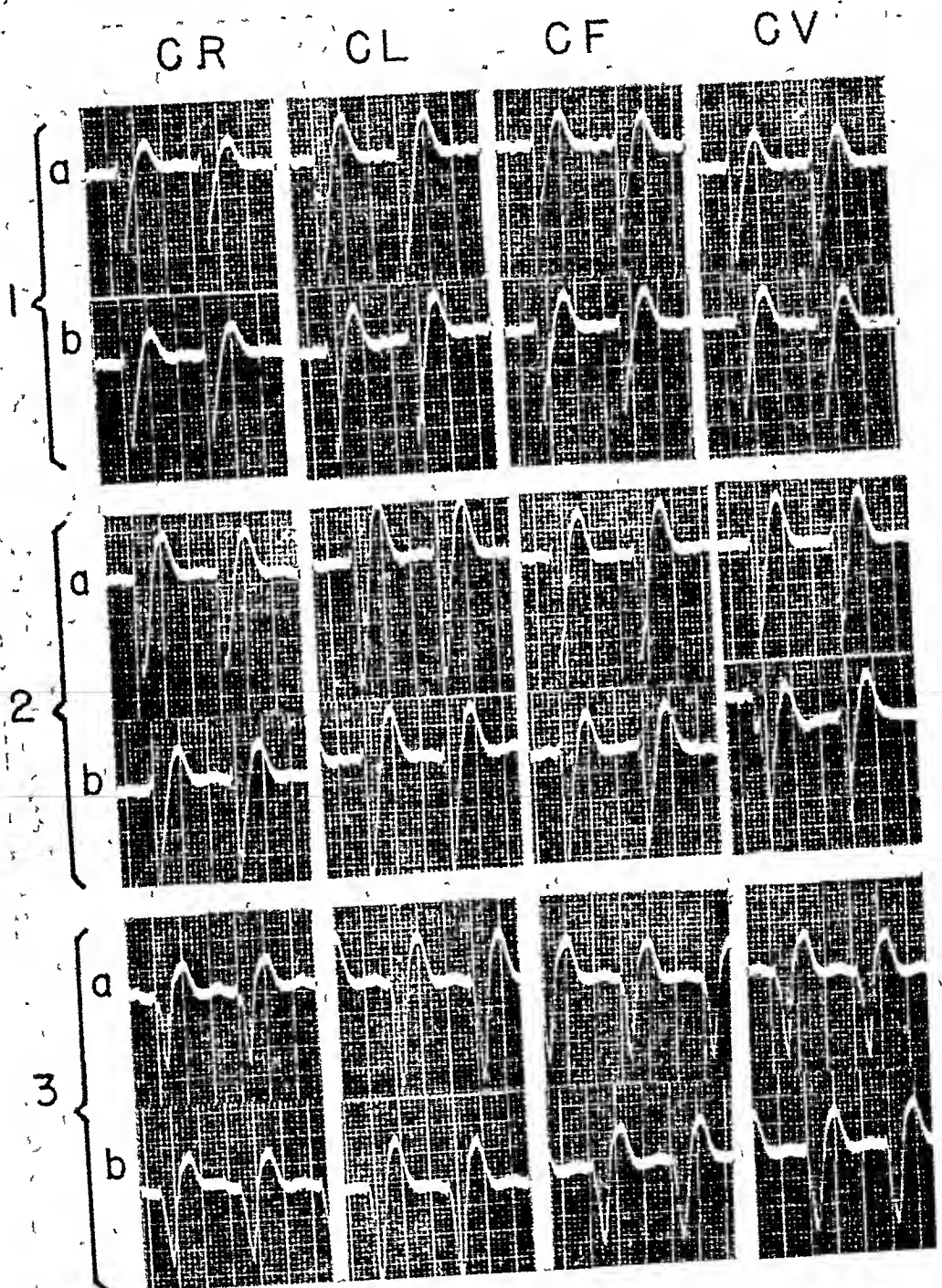


Fig. 7A.

Figs. 7A and 7B.—Patient T. C., whose limb lead electrocardiograms exhibited left bundle branch block.

COMMENT

Six-positional precordial electrocardiograms can be recorded more easily and efficiently by the application to the thorax of an elastic belt carrying six electrodes than by the selective anatomic placement of the chest electrodes for each of the six officially designated precordial positions. Moreover, there is evidence that the precordial belt technique permits fully as good, or better, duplication of results in repetitive examinations than does the conventional technique.

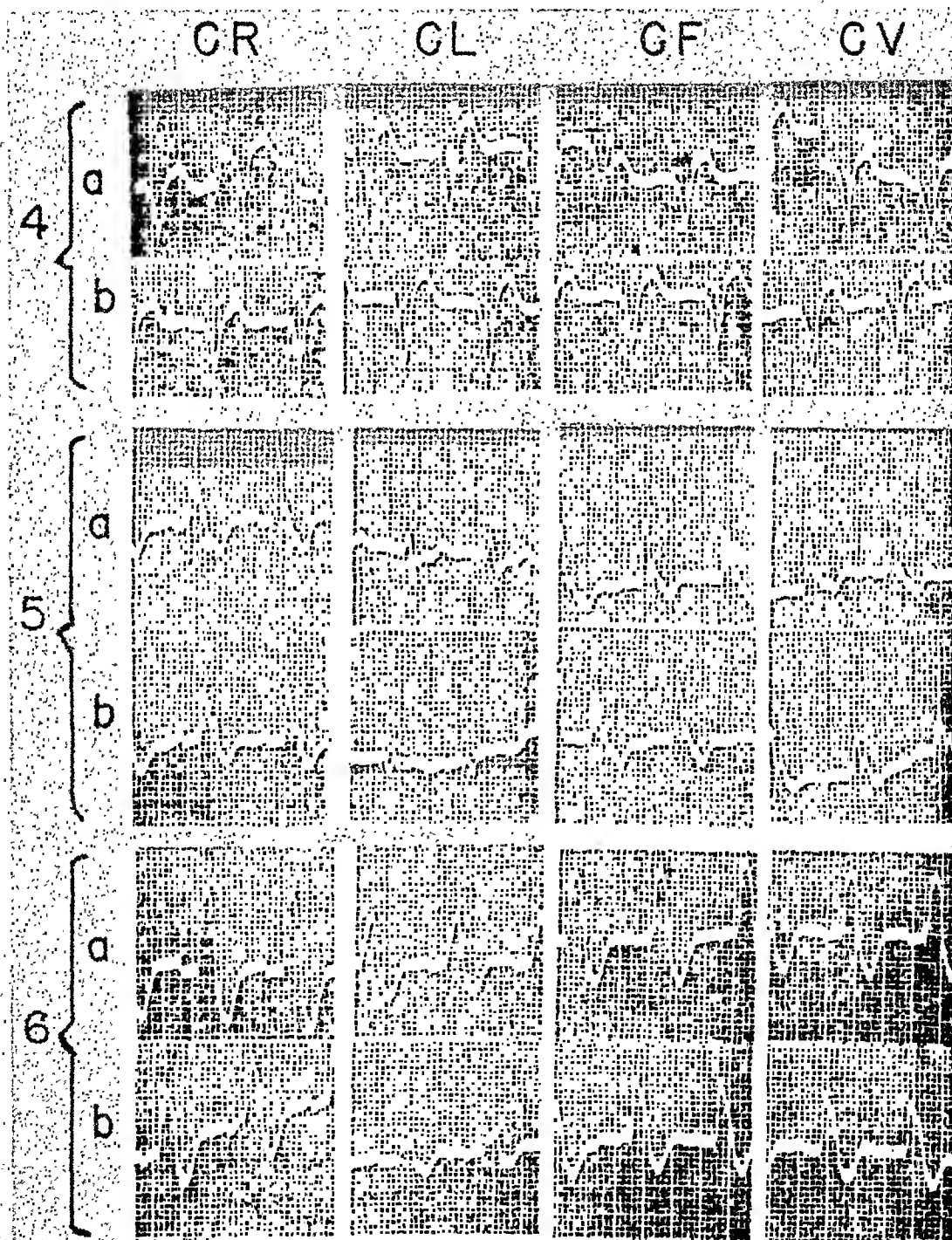


Fig. 7B.—(For legend see Fig. 7A.)

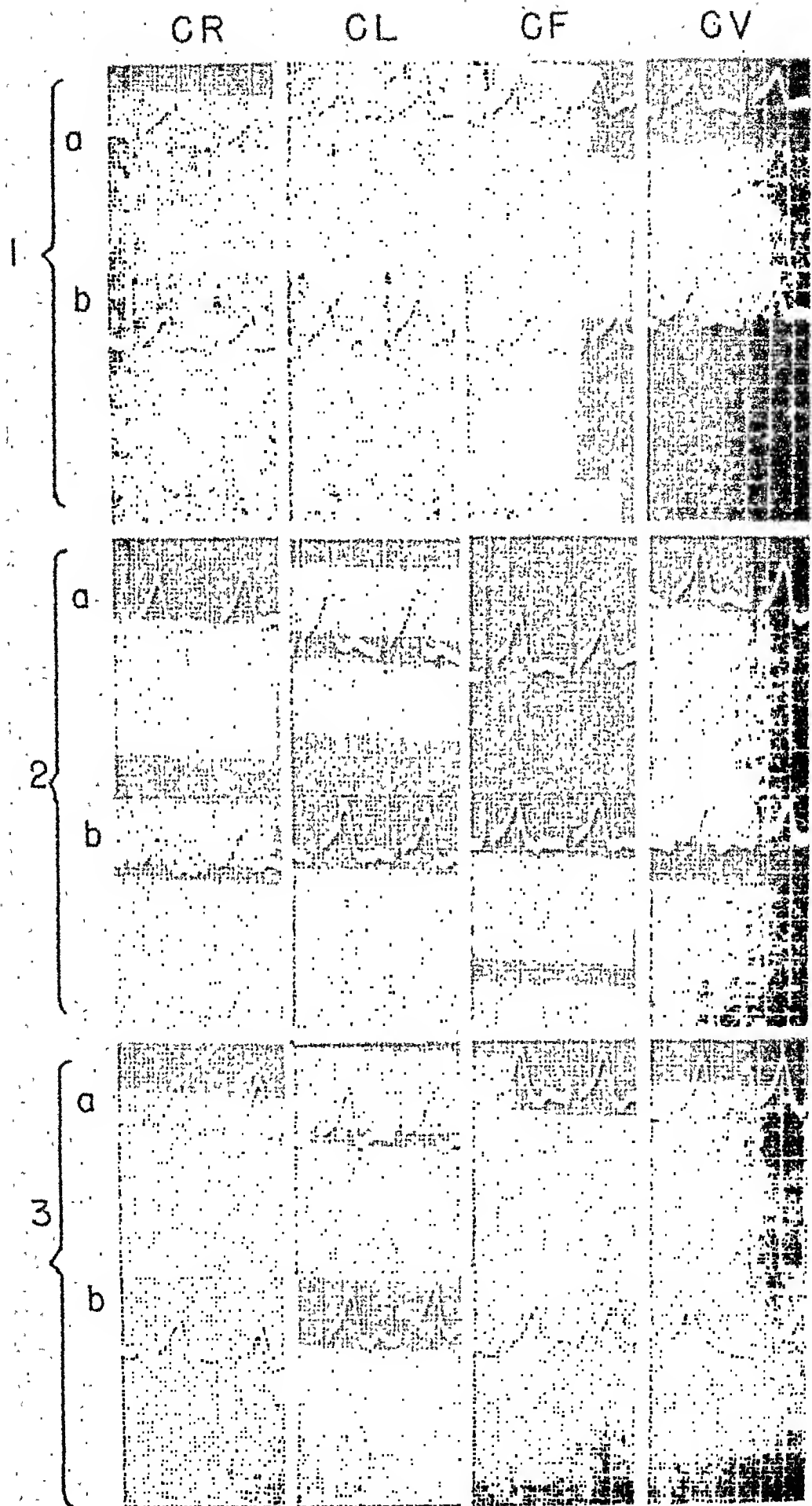


FIG. 8A.—(For legend see Fig. 8B.)

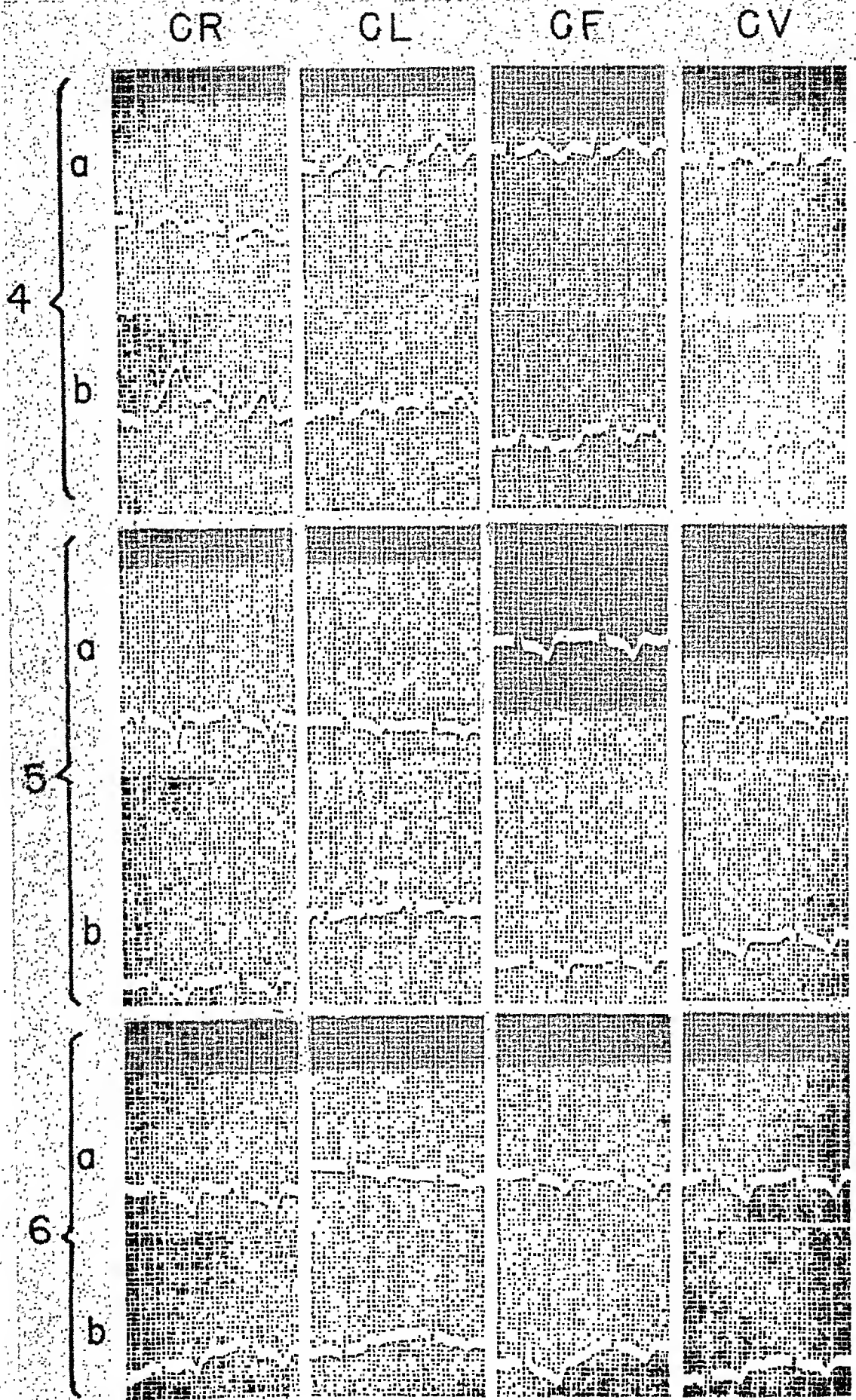


Fig. 8B.

Figs. 8A and 8B.—Patient M. M., whole limb lead electrocardiograms exhibited the pattern of left ventricular hypertrophy and strain.

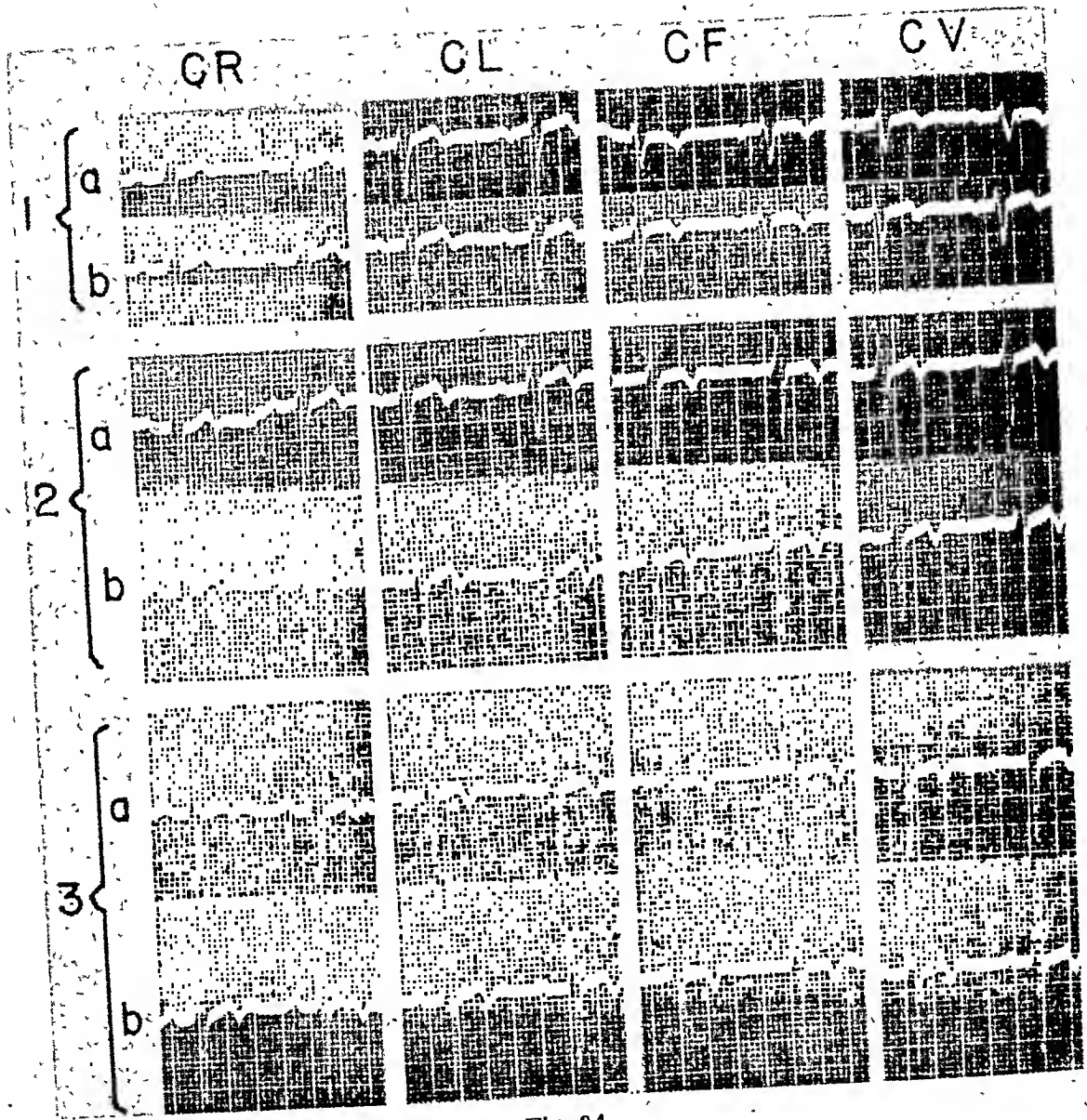


Fig. 9A.

Figs. 9A and 9B.—Patient S. W., with acute myocardial infarction, anterior-apical location.



Fig. 9B.—(For legend see Fig. 9A.)

In applying the electrode belt the technician need find only two easily identified anatomic landmarks (Positions 1 and 6). With the conventional technique it is necessary to identify in addition the other four electrode positions including the important and elusive Position 4, in relation to which Positions 3, 5, and 6 are located. Position 4 is officially defined¹ as the outer border of the apex

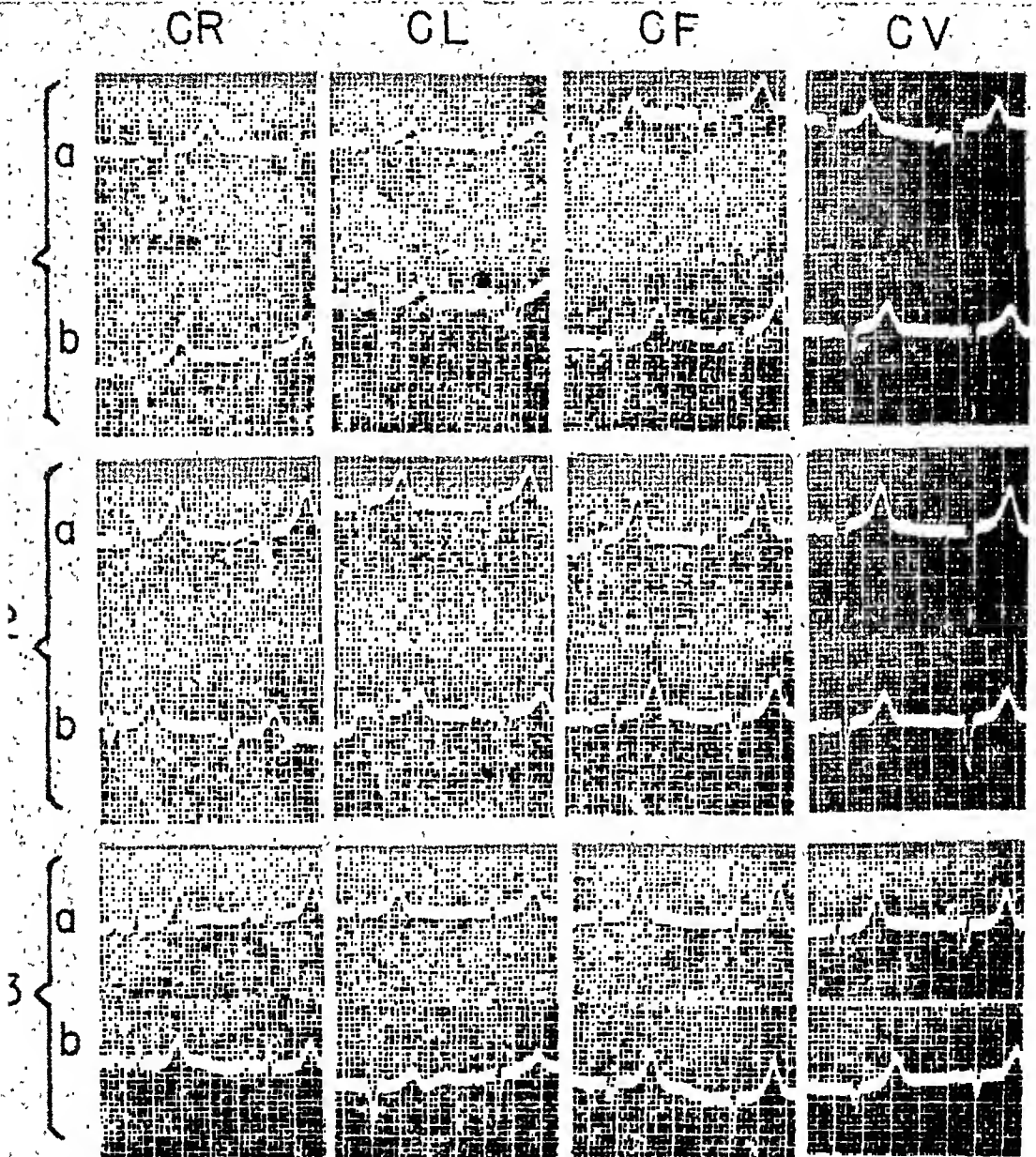


Fig. 10A.

Figs. 10A and 10B.—Patient S. B., with acute myocardial infarction, posterior-basal location.

beat (often undeterminable, especially in chests of emphysematous or obese subjects), or as the point of junction of the fifth intercostal space and the left midclavicular line (not readily determinable with accuracy). The imputed importance of Position 4 in itself and as a reference point for several other posi-

tions, and the improbability that most technicians can reliably identify it, are cogent theoretical objections to the conventional procedure.

One may even question the logic of attempting to place the precordial electrodes in fixed positional relationships to the *heart*. For example, in the electrocardiographic study of cardiac enlargement and displacement, and in the differentiation of right and left bundle branch block by precordial lead ex-

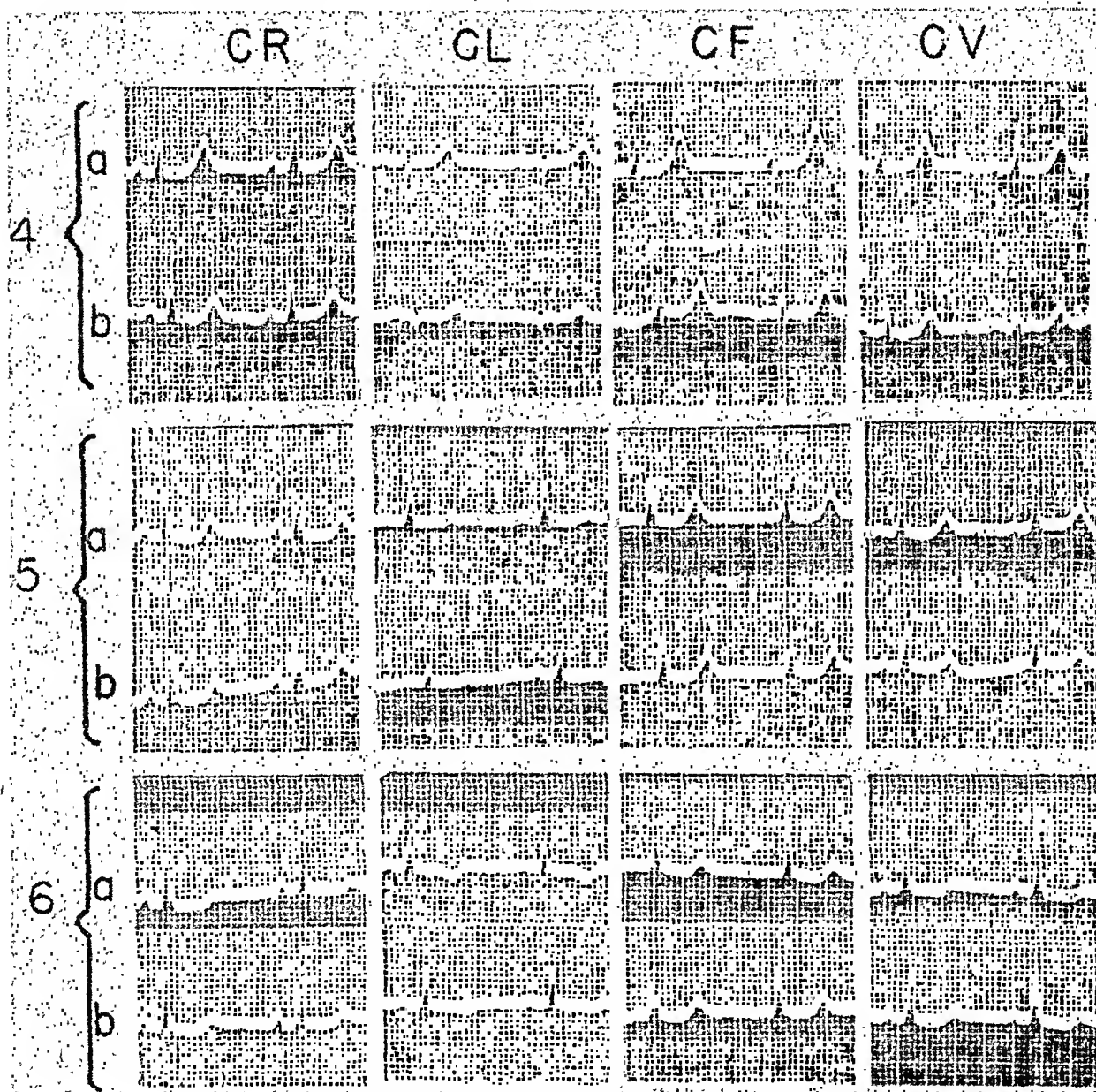


Fig. 10B.—(For legend see Fig. 10A.)

ploration, it would seem that anatomic variations in the total heart mass (and in the right and left ventricular components) would be more reliably revealed by adhering to relatively fixed positions of the electrodes on the *chest wall*. The further discussion of this point is not particularly relevant to the present study and will be the subject of a later report.

Inasmuch as another, though minor, purpose of the precordial belt technique was to shorten the time required to record multiple precordial lead electro-

TABLE IVA. RANGE OF VARIATION IN AMPLITUDES OF DEFLECTIONS OF PRECORDIAL ELECTROCARDIOGRAMS OBTAINED BY THE CONVENTIONAL TECHNIQUE ON TWENTY OCCASIONS IN THE SAME SUBJECT

LEAD POSITION	RANGE OF VARIATION						LEAD CL						LEAD OF						LEAD CV					
	LEAD CR						RANGE OF VARIATION						RANGE OF VARIATION						RANGE OF VARIATION					
	R	S	T				R	S	T				R	S	T				R	S	T			
1	2-4	7-14	3-7				1-2	8-16	1-5*				1-2	11-18	1½-4				1-2½	8-16				
2	3-7	9-14	6-10				2-3½*	10-19	4-9				2-3½	12-20	3-8				2-4*	10-18				
3	5-16	7-14	8-13				3-10	6-14	6-10*				3-10	7-15	6-10				4-13	7-13				
4	11-26	4-10	5-11				7-16	3-8	5-10				5-16	3-9	4-10				7-17	3-10				
5	12-20	1-4*	5-8*				8-13	1-4*	3-6				5-11	0-4*	2-5				8-15	½-4				
6	11-14	0-2*	4-6				6-10	0-2*	1½-4*				3-7	0-1*	½-2				7-10	0-1*				

*Denotes features in which there was less variation with the conventional technique than with the other.

TABLE IVB. RANGE OF VARIATION IN AMPLITUDES OF DEFLECTIONS OF PRECORDIAL ELECTROCARDIOGRAMS OBTAINED BY THE BELT TECHNIQUE ON TWENTY OCCASIONS IN THE SAME SUBJECT

LEAD POSITION	RANGE OF VARIATION						LEAD CL						LEAD OF						LEAD CV					
	RANGE OF VARIATION						RANGE OF VARIATION						RANGE OF VARIATION						RANGE OF VARIATION					
	R	S	T				R	S	T				R	S	T				R	S	T			
1	2-4	7-12*	4-7*				1-2	9-15*	1-5½				1-2	11-17*	½-4				1-2*	9-15*				
2	4-7*	9-14	7-11				2-4	8-14*	4-9				2-3*	10-16*	3-8				2-5	10-16*				
3	5-16	4-11	7-11*				3-10	4-10*	5-10				3-10	5-10*	5-9				4-13	5-10*				
4	11-21*	3-8*	7-12*				7-14*	3-8	5-10				7-16	2-7*	3-8*				7-16*	3-8*				
5	12-18*	1-6	4-9				7-12	1-5	3-6				5-11	½-5	2-5				8-14*	½-4				
6	11-14	1-4	4-6				6-10	½-4	2-6				5-8*	0-3	1-2½				8-11	½-4				

*Denotes features in which there was less variation with the belt technique than with the other.

cardiograms, the two techniques were timed during recordings of the CF₁₋₆ series. With the aid of the precordial belt, the recording was accomplished in approximately two-thirds of the time required for the conventional procedure.

It is hoped that the advantages of the technique described will encourage freer and wider routine recording of multiple precordial electrocardiograms, and that through such greater experience the knowledge and clinical value of this important aspect of electrocardiography will develop more rapidly and along more uniform lines.

SUMMARY

1. A simple, rapid, and clinically valid technique is described for recording multiple precordial lead electrocardiograms.

2. The technique employs an elastic belt carrying six precordial electrodes; for the placement of these only the first and sixth precordial positions need be defined.

3. With this procedure the precordial electrode placements are distributed equidistantly over the precordium. Certain theoretical advantages of such placements that are in fixed relation to the thorax, rather than to the heart, are discussed briefly.

REFERENCES

1. a. Standardization of Precordial Leads; Joint Recommendations of the American Heart Association and the Cardiac Society of Great Britain and Ireland, AM. HEART J. 15: 107, 1938.
b. Supplementary Report, AM. HEART J. 15: 235, 1938.

INFLUENCE OF VARIATIONS IN ATMOSPHERIC TEMPERATURE
AND HUMIDITY, ON THE RATES OF WATER AND HEAT
LOSS FROM THE RESPIRATORY TRACT OF PATIENTS
WITH CONGESTIVE HEART FAILURE LIVING
IN A SUBTROPICAL CLIMATE

G. E. BURCH, M.D.*
NEW ORLEANS, LA.

STUDIES of the rates of water and heat loss from the respiratory tract of patients with congestive heart failure were reported previously.¹ These observations were limited entirely to comfortable atmospheric conditions. Since man finds himself, both during health and disease, in atmospheric conditions of great variations, it was considered of interest to know how certain variations in atmospheric temperature and humidity influence the rates of water and heat loss from the respiratory tract of patients suffering with congestive heart failure. This is of particular importance when it is realized that extreme variations in environmental conditions will precipitate congestive heart failure.^{1, 2} It was noted in these two studies that a hot and humid environment would precipitate an acute attack of cardiac asthma associated with apprehension and panic. A knowledge of the effects of such an environment on the rates of water and heat loss would aid in understanding the influences of a hot and warm atmosphere upon the management of congestive heart failure.

METHODS AND MATERIALS

The methods employed for the measurement of the rates of water and heat loss have been described.^{1, 3} The subjects consisted of thirteen patients with moderate Functional Class IV⁴ congestive heart failure of both right and left ventricular types. These patients were all bedridden and under essentially the same standard form of treatment for their uncomplicated heart failure. They were transported from their hospital bed to the laboratory for study. They rested in the laboratory at least thirty minutes before any observations were commenced and remained comfortably seated in a chair throughout the study. They were clothed in an ordinary type of cotton hospital gown and covered with a cotton sheet from the waist down.

The patients were first studied in a *cool foggy* atmosphere: the mean temperature was 13.9° C. (extremes, 10.5 and 16.1) and the mean relative humidity was 94 per cent (extremes, 89 and 100). The room conditions were then changed to make it comfortable: the mean temperature was raised to 20.3° C. (extremes, 19.7 and 21.1) and relative humidity was lowered to 58 per cent (extremes, 54

Aided by a grant from the Rockefeller Foundation, and the Helis Institute for Medical Research.

Received for publication Dec. 12, 1945.

*From the Department of Medicine, Tulane Medical School, and the Charity Hospital, New Orleans.

and 67). The room conditions were then changed to make it *warm*, with a mean temperature of 35.7°C . (extremes, 35 and 36.6) and a relative humidity of 56 per cent (extremes, 50 and 65). The temperature of the room was made *slightly warmer*: the mean temperature was 38.4°C . (extremes, 37.7 and 38.9) and relative humidity was 49.2 per cent (extremes, 41 and 56). Higher room temperatures could not be employed as they resulted in marked discomfort with apprehension, increase in dyspnea, and, at times, even acute cardiac asthma. Measurements of the rates for water and heat loss were repeated for all four atmospheric conditions in succession in most of the subjects. Measurements were checked on another day, usually the next.

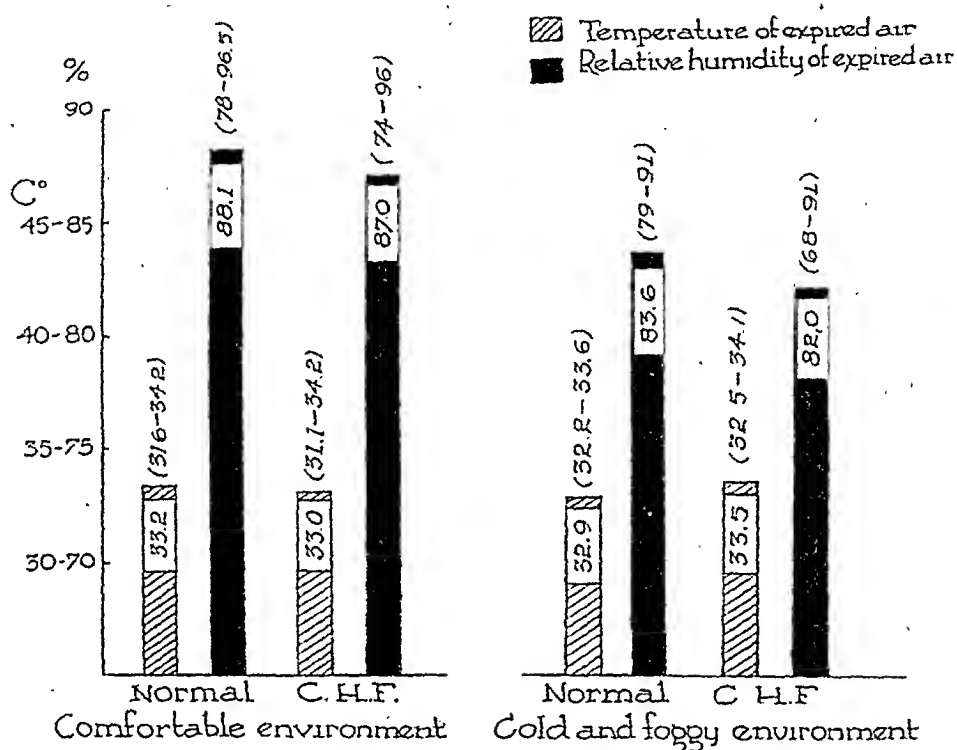


Fig. 1.—The temperature and relative humidity of the expired air of normal subjects and patients with right and left ventricular congestive heart failure (Functional Class IV). The subjects rested, sitting quietly in a comfortable, and a cold and foggy room atmosphere. The mean values are shown within the columns and the extremes are shown within the parenthesis above the columns.

RESULTS

The results are summarized in detail in Tables I, II, III, and IV, and Figs. 1, 2, and 3. Fig. 2 should be consulted for comparison with normal values reported elsewhere.¹ The statistical constants are shown in the tables.

Temperature of the Expired Air.—*Relative Humidity of the Expired Air:* The mean relative humidity of the expired air when the room atmosphere was cool and foggy was 82 per cent (extremes, 68 and 91). The values changed to 84.5 per cent (extremes, 74 and 96) when the room was made comfortable. Upon increasing the room temperature to 35.7°C . the relative humidity of the expired air was 89 per cent (extremes, 84 and 93). When the room atmosphere was made slightly drier and warmer the relative humidity of the air expired became 85 per cent (extremes, 77 and 91). Consult Tables I through IV for details.

Rate of Water Loss From the Respiratory Tract.—The mean rate of water loss was 0.961 Gm. per square meter of body area per ten minutes (extremes, 0.5839 and 1.3255) when the room environment was cool and foggy. When the room atmosphere was comfortable, the mean rate was 0.931 (extremes, 0.497 and 1.482). Upon increasing the room temperature to make the environment warm (35.7° C.) the mean rate of loss was 0.952 (extremes, 0.660 and 1.208). When the room atmosphere was made slightly warmer and drier the rate became 0.798 (extremes, 0.456 and 0.973).

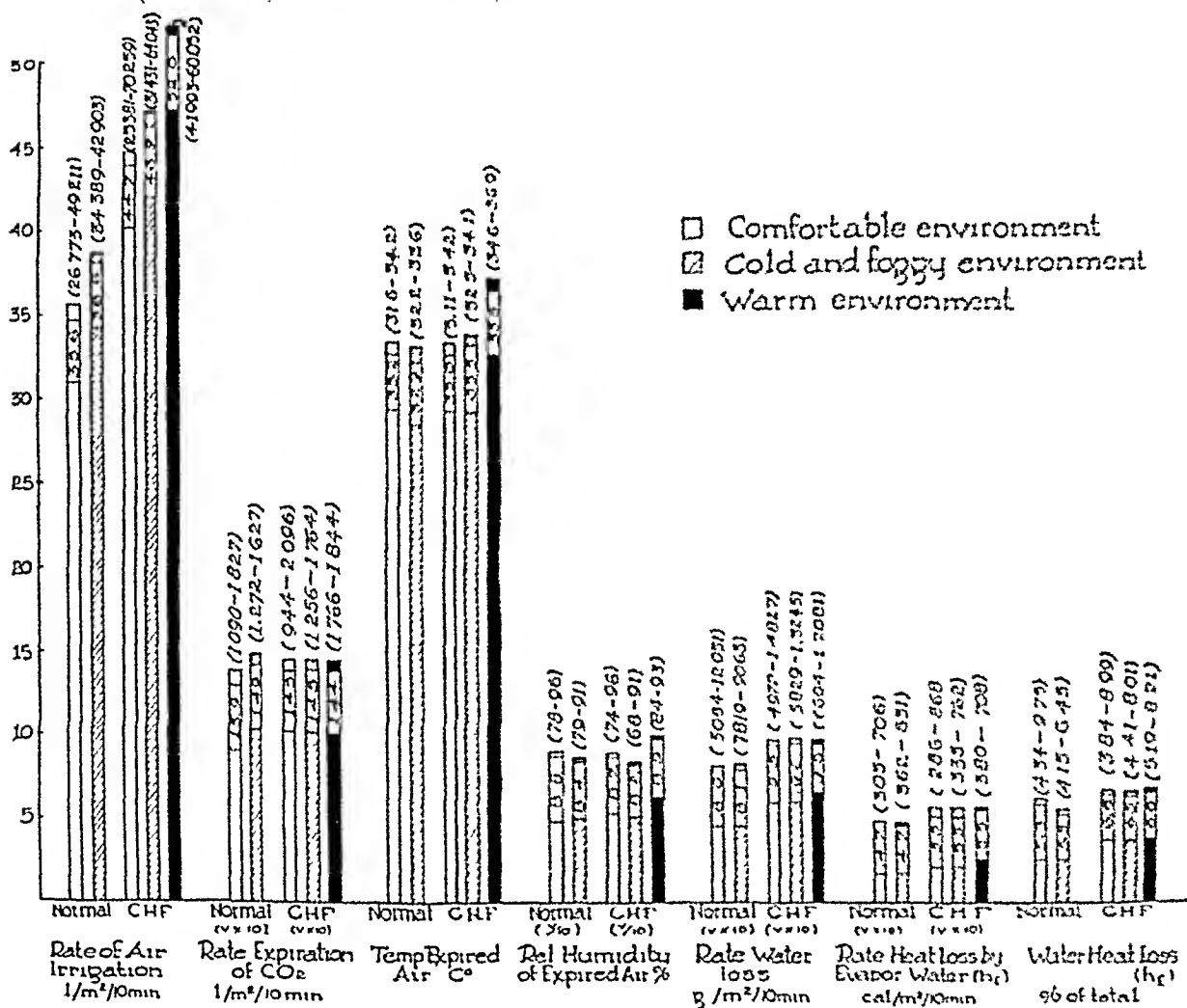


FIG. 2A.

Figs. 2A and 2B.—The relationships of the rates of water and heat losses from the respiratory tract in patients with right and left ventricular congestive heart failure (Functional Class IV) under various environmental conditions. All patients rested sitting quietly. In order to use a common ordinate, the true values (V) were recorded as multiples of ten. The actual values are indicated with the means within the columns and the ranges in parentheses above the columns. The figure was broken into parts A and B for convenience. All measurements were made simultaneously for each subject at each condition of the room air.

Rate of Irrigation of the Respiratory Tract With Air.—The mean rate of irrigation of the respiratory tract with air was 46.860 liters per square meter of body area per ten minutes (extremes, 31.431 and 64.043) when the environment was cool and foggy. When the room conditions were made comfortable, the mean rate became 44.833 (extremes, 25.381 and 70.259). Upon raising the

room temperature to 35.7° C., the mean rate was 51.991 (extremes, 41.993 and 60.052). In a slightly warmer and drier atmosphere, the mean value was 49.588 (extremes, 28.003 and 59.295).

There was a high positive correlation between the rate of irrigation of the respiratory tract with air and the rate of water loss (Fig. 3). This was true for all four environmental conditions and is in keeping with similar findings for comfortable environments in normal subjects and patients with congestive heart failure.^{1, 2} From Fig. 3, it is noted that the correlation tends to be slightly lower under conditions of the warm environment.

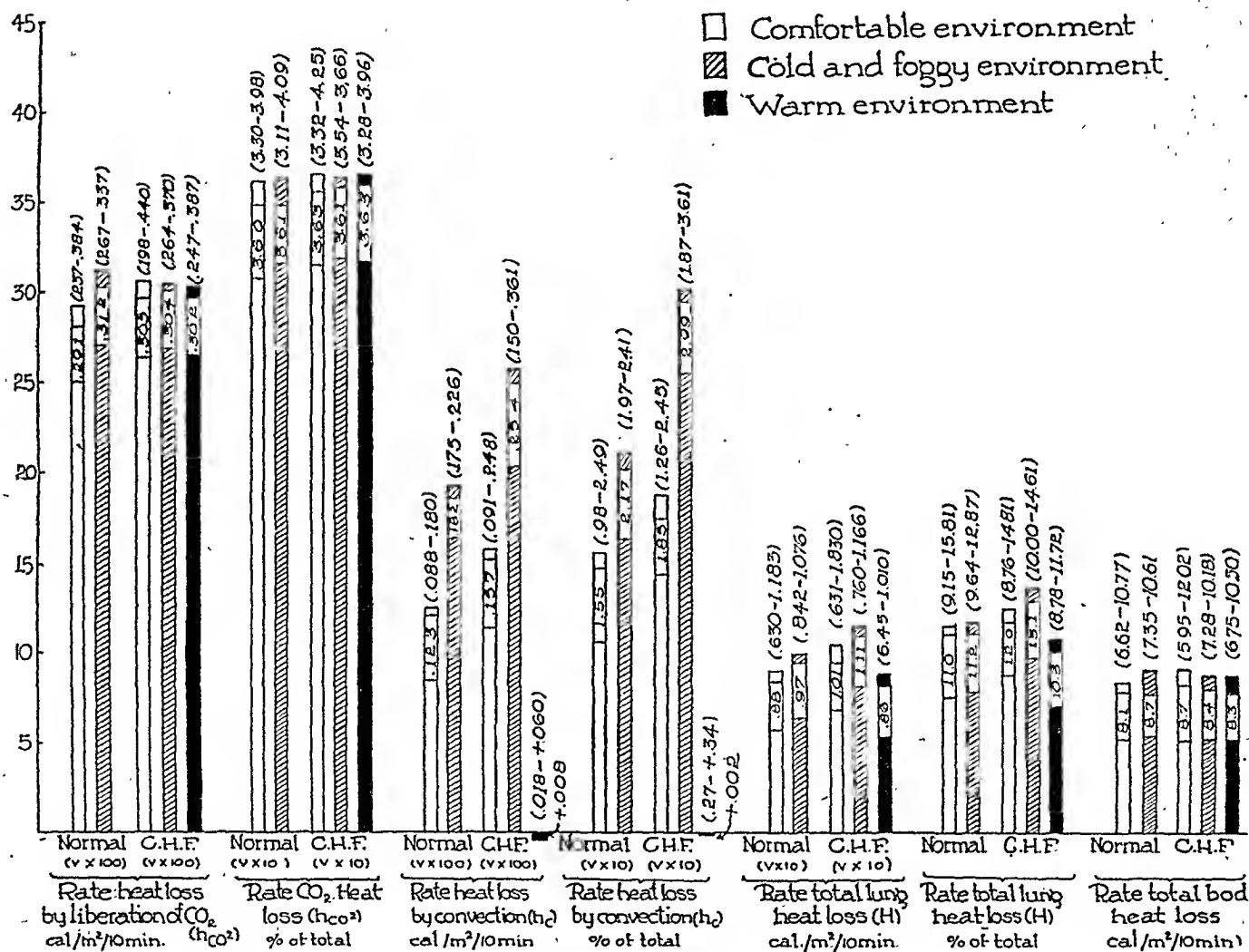


Fig. 2B.—(For legend see Fig. 2A.)

Rates of Heat Loss From the Respiratory Tract.—

1. Rate of Heat Loss From the Vaporization of Water, h_E : When the room environment was cool and foggy, the mean rate of heat loss by vaporization of water (h_E) was 0.553 calorie per square meter of body area per ten minutes (extremes, 0.335 and 0.762). This represented 6.54 per cent of the total body heat loss or 49.8 per cent of the total heat loss from the respiratory tract. The mean rate of heat loss from the vaporization of water was 0.539 calorie per square meter of body area per ten minutes (extremes, 0.286 and 0.868) when

the room atmosphere was comfortable. This represented about 6.48 per cent of the total loss of body heat or 62.7 per cent of the total heat lost from the respiratory tract.

When the room temperature was increased and the room was made warm (35.7° C.) the mean rate of heat loss (h_r) was 0.552 calorie per square meter of body area per ten minutes (extremes, 0.380 and 0.708). This represented 6.64 per cent of the total heat lost from the body or 64.3 per cent of the total heat lost from the respiratory tract. Upon making the room slightly warmer and drier the mean rate became 0.461 calorie (extremes, 0.262 and 0.560). This represented 5.39 per cent of the total heat loss or 62.3 per cent of the total heat lost from the respiratory tract.

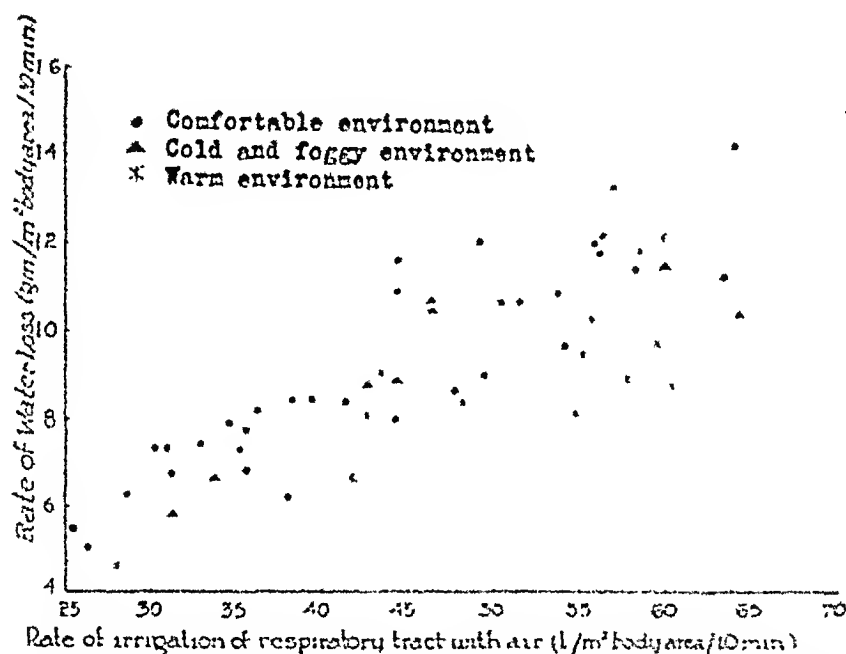


Fig. 3.—A spot graph to illustrate the high correlation of the rate of irrigation of the respiratory tract with air and the rate of water loss from the respiratory tract. The patients with right and left ventricular congestive heart failure (Functional Class IV) rested sitting quietly. The correlation was greater at the cold and comfortable environmental atmospheric conditions than at the warm ones.

2. Rate of Heat Loss From the Decomposition of Carbonic Acid and the Excretion of Carbon Dioxide, h_{CO_2} : The mean rate of heat loss from the expiration of carbon dioxide, h_{CO_2} , was 0.304 calorie per square meter of body area per ten minutes (extremes, 0.264 and 0.370) when the environment was cool and foggy. This represented 3.61 per cent of the total body heat loss or 27.4 per cent of the total loss from the respiratory tract. When the room atmosphere was made comfortable, the mean rate of heat loss (h_{CO_2}) was 0.293 calorie (extremes, 0.225 and 0.387). This represented 3.58 per cent of the total loss of body heat or 31.9 per cent of total heat loss from the respiratory tract.

When the room temperature was increased to produce a warm atmosphere (35.7° C.), the mean rate was 0.302 calorie (extremes, 0.247 and 0.387). This represented 3.63 per cent of the total heat lost from the body or 36.2 per cent

of the total heat lost from the respiratory tract. When the room environment was made slightly warmer and drier, the mean rate of heat loss was 0.315 calorie (extremes, 0.272 and 0.361). This represented 3.69 per cent of the total heat lost from the body or 42.6 per cent of the total lost from the respiratory tract.

3. Rate of Heat Loss by Convection, Warming Inspired Air, h_c . When the room environment was made cool and foggy the mean rate of heat loss by warming inspired air, h_c , was 0.254 calorie per square meter of surface area per ten minutes (extremes, 0.150 and 0.361). This represented 2.99 per cent of the total heat lost from the body or 22.9 per cent of the total lost from the respiratory tract. When the room atmosphere was made comfortable, the mean rate was 0.162 calorie (extremes, 0.091 and 0.248). This represented 1.95 per cent of the total heat lost from the body or 17.6 per cent of the total heat lost from the respiratory tract.

When the room atmosphere was made warm (35.7°C.) there was a slight mean gain in heat, by expiring cooler air, of 0.008 calorie per square meter of body area per ten minutes (extremes, -0.018 and $+0.060$). This represented 0.002 per cent of the total heat lost from the body or 0.2 per cent of the total loss from the respiratory tract. When the room atmosphere was made slightly warmer and drier there was a mean gain of 0.036 calorie (extremes, $+0.019$ and $+0.051$). This represented 0.004 per cent of the total heat lost from the body or 0.5 per cent of the total lost from the respiratory tract.

4. The Rate of Total Heat Loss From the Respiratory Tract, H : In the cool and foggy environment, the mean rate of total heat loss from the respiratory tract, H , was 1.111 calories per square meter of body surface per ten minutes (extremes 0.760 and 1.166). This represented 13.2 per cent of the total heat lost from the body. When the room conditions were made comfortable the mean rate was 0.918 calorie (extremes, 0.631 and 1.503) or 11.2 per cent of the total rate of heat lost from the body. Upon making the room atmosphere warm (35.7°C.) the mean rate became 0.858 calorie (extremes, 0.645 and 1.010) or 10.3 per cent of the total body heat loss. When the room air was made slightly warmer and drier the mean rate became 0.740 calorie (extremes, 0.515 and 0.835) or 8.7 per cent of the total body heat loss.

5. The Rate of Total Loss of Body Heat: The mean rate of total body heat loss in the cool and foggy environment was 8.43 calories per square meter of surface area per ten minutes (extremes 7.28 and 10.18). When the environment was comfortable the rate was 8.20 calories (extremes, 6.56 and 10.50). Upon making the room air warm (35.7°C.) the rate of total body heat loss was 8.34 calories (extremes, 6.75 and 10.50). The value became 8.52 calories (extremes, 7.51 and 9.53) in a slightly warmer and drier atmosphere.

General Reactions.—All patients did not enjoy the comfortable environmental conditions. Most of them found the cool and foggy atmosphere uncomfortably cool and would not like to remain under such conditions too long. In some instances, the patients insisted on covering themselves with woolen blankets. The patients did not object to the warm environments, and some of the Negro patients even preferred them. They all admitted that the temperature was too

TABLE I. THE RATES OF WATER AND HEAT LOSSES FROM THE RESPIRATORY TRACT OF NINE CLASS IV). THE SUBJECTS RESTED SITTING

SUBJECT	AGE (YR.)	SEX	RACE	ENVIRONMENTAL AIR		AIR IRRIGATING LUNGS	CO ₂ EXHALED	EXPIRED AIR	
				D.B.† ° C.	R.H.‡ %			D.B.† ° C.	R.H.‡ %
1	31	M	N	16.1	89	31.431	1.307	33.7	82
2	27	F	N	15.3	97	46.335	1.310	33.6	91
3	44	F	W	14.2	97	44.232	1.266	33.6	79
4	53	F	N	15.5	89	30.370	1.398	33.6	86
5	41	F	N	14.4	94	46.277	1.502	33.9	88
6	49	M	W	13.3	94	64.043	1.764	33.6	68†
7	66	F	N	12.2	100	56.752	1.751	34.1	83
8	35	M	N	10.5	90	42.474	1.256	32.5	78
9	56	M	N	13.3	100	59.853	1.481	32.7	79
Mean				13.9	94	46.860	1.448	33.5	82
Standard deviation						11.668±	0.112±	0.4±	6.8±
Coefficient of variation						2.750	0.026	0.09	0.16
Range						24.9±	7.73±	1.19±	8.24±
						5.87%	1.82%	0.28%	1.94%
				10.5	89	31.431	1.256	32.5	68
				16.1	100	64.043	1.764	34.1	91

*These units are measured in square meters per ten minutes.

†D.B. = Dry bulb.

‡R.H. = Relative humidity.

TABLE II. THE RATES OF WATER AND HEAT LOSSES FROM THE RESPIRATORY TRACT OF TEN CLASS IV). THE SUBJECTS RESTED SITTING

SUBJECT	AGE (YR.)	SEX	RACE	ENVIRONMENTAL AIR		AIR IRRIGAT- ING LUNGS	CO ₂ EXHALED	EXPIRED AIR		WATER LOSS GM./M. ² / 10*
				D.B.†	R.H.‡			D.B.†	R.H.‡	
1	31	M	N	21.1	55	35.112	1.072	34.0	82	0.6575
2	27	F	N	20.0	67	48.909	1.437	34.1	96	1.2034
3	44	F	W	20.3	63	44.232	1.446	33.7	79	0.8000
4	53	F	N	19.7	57	47.897	1.446	33.6	86	0.8773
				20.5	57	25.381	1.075	33.6	83	0.5421
				20.3	57	26.350	1.294	33.6	77	0.4972
5	41	F	N	21.1	64	44.333	1.502	33.9	88	0.9442
6	49	M	W	19.7	59	53.972	1.579	33.9	74	0.9638
8	35	M	N	20.0	57	35.619	1.256	33.6	81	0.6801
10	67	M	N	20.0	54	55.908	1.464	33.1	82	1.2063
11	52	M	N	20.3	56	44.204	1.442	33.6	91	1.0940
12	54	M	N	20.0	55	70.259	1.844	32.9	87	1.4817
Mean				20.3	58	44.883	1.398	33.5	84.5	0.9306
Range				19.7	54	25.381	1.072	32.5	74	0.4972
				21.1	67	70.259	1.844	34.1	96	1.4917
Standard deviation						12.42±	0.19±	0.49±	6.5±	0.35±
Coefficient of variation						2.44	0.04	0.10	1.3	0.07
						27.6±	13.6±	1.46±	7.6±	37.6±
						5.4%	2.7%	0.28%	1.5%	10.4%

*These units are measured in square meters per ten minutes.

†D.B. = Dry bulb.

‡R.H. = Relative humidity.

PATIENTS WITH RIGHT AND LEFT VENTRICULAR CONGESTIVE HEART FAILURE (FUNCTIONAL
QUIETLY IN A COLD AND FOGGY ROOM ATMOSPHERE

WATER LOSS	RATE OF HEAT LOSS									TOTAL HEAT LOSS
	WATER VAPORIZED		LIBERATION OF CO ₂		WARMING AIR		TOTAL LOSS FROM LUNGS		CAL./M. ² / 10*	
	CAL./M. ² / 10*	% TOTAL	CAL./M. ² / 10*	% TOTAL	CAL./M. ² / 10*	% TOTAL	CAL./M. ² / 10*	% TOTAL		
GM./M. ² / 10*	CAL./M. ² / 10*		CAL./M. ² / 10*		CAL./M. ² / 10*		CAL./M. ² / 10*		CAL./M. ² / 10*	
0.5829	0.335	4.41	0.274	3.61	0.151	1.99	0.760	10.00	7.59	
1.0692	0.615	8.01	0.275	3.58	0.232	3.02	1.122	14.61	7.68	
0.8910	0.512	6.81	0.266	3.54	0.235	3.13	1.013	13.47	7.52	
0.6676	0.384	4.78	0.294	3.66	0.150	1.87	0.828	10.31	8.03	
1.0504	0.604	6.97	0.315	3.63	0.247	2.85	1.166	13.45	8.67	
1.0397	0.598	5.87	0.370	3.63	0.361	3.55	1.329	13.06	10.18	
1.3245	0.762	7.52	0.368	3.63	0.340	3.36	1.470	14.51	10.13	
0.8837	0.508	6.98	0.264	3.63	0.255	3.50	1.027	14.11	7.28	
1.1437	0.658	7.49	0.312	3.55	0.317	3.61	1.287	14.66	8.78	
0.9614	0.553	6.54	0.304	3.61	0.254	2.99	1.111	13.13	8.43	
0.3413±	0.125±	1.24±	0.040±	0.041±	0.074±	0.673±	0.226±	1.65±	1.14±	
0.057	0.029	0.29	0.009	0.010	0.017	0.159	0.053	0.38	0.27	
25.10±	22.586±	19.02±	13.16±	1.14±	29.13±	22.51±	20.34±	12.58±	13.50±	
5.92%	5.324%	4.48%	1.31%	0.27%	6.18	5.31	4.79	2.97	3.18	
0.5829	0.335	4.41	0.264	3.54	0.150	1.87	0.760	10.00	7.28	
1.3245	0.762	8.01	0.370	3.66	0.361	3.61	1.166	14.61	10.18	

PATIENTS WITH RIGHT AND LEFT VENTRICULAR CONGESTIVE HEART FAILURE (FUNCTIONAL
QUIETLY IN A COMFORTABLE ROOM ATMOSPHERE

RATE OF HEAT LOSS								
WATER VAPORIZED		LIBERATION OF CO ₂		WARMING AIR		TOTAL LOSS FROM LUNGS		TOTAL BODY HEAT LOSS
CAL./M. ² / 10*	% TOTAL	CAL./M. ² / 10*	% TOTAL	CAL./M. ² / 10*	% TOTAL	CAL./M. ² / 10*	% TOTAL	CAL./M. ² / 10*
0.378	5.40	0.225	3.21	0.124	1.77	0.727	10.39	7.00
0.692	8.41	0.302	3.67	0.188	2.28	1.182	14.36	8.23
0.460	5.41	0.304	3.58	0.162	1.91	0.926	10.89	8.50
0.504	6.09	0.304	3.67	0.182	2.20	0.990	11.96	8.28
0.312	4.76	0.228	3.48	0.091	1.39	0.631	9.62	6.56
0.286	3.84	0.272	3.65	0.096	1.29	0.654	8.78	7.45
0.543	6.18	0.315	3.59	0.155	1.77	1.013	11.54	8.78
0.554	5.89	0.332	3.53	0.201	2.23	1.096	11.66	9.40
0.391	5.37	0.264	3.63	0.132	1.81	0.787	10.81	7.28
0.707	8.29	0.307	3.60	0.200	2.34	1.214	14.23	8.53
0.641	7.60	0.303	3.59	0.161	1.91	1.105	13.11	8.43
0.868	8.27	0.387	3.69	0.248	2.36	1.503	14.31	10.50
0.539	6.48	0.293	3.58	0.162	1.95	0.918	12.00	8.20
0.286	3.84	0.225	3.21	0.091	1.29	0.631	8.78	6.56
0.868	8.73	0.387	3.69	0.248	2.36	1.503	14.36	10.50
0.174±	1.60±	0.042±	0.12±	0.033±	0.344±	0.21±	2.2±	0.99±
0.034	0.31	0.008	0.02	0.006	0.067	0.04	0.4	0.19
32.3±	24.7±	14.3±	3.0±	20.3±	21.23±	22.8±	18.5±	11.9±
6.3%	4.9%	2.8%	0.6%	3.9%	4.1%	4.5%	3.6%	2.3%

TABLE III. THE RATES OF WATER AND HEAT LOSSES FROM THE RESPIRATORY TRACT OF EIGHT CLASS IV). THE PATIENTS RESTED SITTING

				ENVIRONMENTAL AIR		AIR IRRIGAT- ING LUNGS	CO ₂ EXHALED	AIR EXPIRED		WATER LOSS
SUBJECT	AGE (YR.)	SEX	RACE	D.B.† ° C.	R.H.‡ %	L./M. ² /10*	L./M. ² /10*	D.B.† ° C.	R.H.‡ %	GM./M. ² / 10*
1	31	M	N	35.0	65	41.993	1.176	36.6	84	0.6604
2	27	F	N	35.5	54	54.977	1.310	36.4	93	0.9432
6	49	M	W	36.6	61	60.052	1.671	34.6	88	0.8788
7	66	F	N	36.1	56	58.066	1.400	36.9	89	1.1776
8	35	M	N	35.0	50	43.368	1.242	35.4	87	0.9075
10	67	M	N	35.6	50	59.661	1.488	35.0	90	1.2081
11	52	M	N	35.6	55	42.474	1.383	36.1	88	0.8113
12	54	M	N	36.4	59	55.400	1.844	35.3	89	1.0289
Mean				35.7	56	51.991	1.439	35.8	89	0.9520
Range				35.0	50	41.993	1.176	34.6	84	0.6604
				36.6	65	60.052	1.844	36.9	93	1.2081
Standard deviation						7.999±	0.219±	0.83±	2.6±	0.269±
Coefficient of variation						2.000	0.005	0.207	0.66	0.087
						15.39±	15.22±	2.31±	2.94±	28.26±
						3.85%	3.81%	0.58%	0.73%	7.07%

*These units are measured in square meters per ten minutes.

†D.B. = Dry bulb.

‡R.H. = Relative humidity.

TABLE IV. THE RATES OF WATER AND HEAT LOSSES FROM THE RESPIRATORY TRACT OF FIVE CLASS IV). THE PATIENTS RESTED SITTING QUIETLY

				ENVIRONMENTAL AIR		AIR IRRIGATING LUNGS	CO ₂ EXHALED	AIR EXPIRED		WATER LOSS
SUBJECT	AGE (YR.)	SEX	RACE	D.B.† ° C.	R.H.‡ %	L./M. ² /10*	L./M. ² /10*	D.B.† ° C.	R.H.‡ %	GM./M. ² / 10*
3	44	F	W	37.7	52	59.295	1.356	36.1	86	0.9733
4	53	F	N	38.6	52	28.003	1.294	36.1	94	0.4560
5	41	F	N	38.6	56	57.937	1.719	36.1	91	0.8931
9	56	M	N	38.3	41	54.598	1.484	35.5	77	0.8230
13	35	M	N	38.9	45	48.107	1.636	35.0	88	0.8445
Mean				38.4	49.2	49.588	1.498	35.8	85	0.7980
Range				37.7	41	28.003	1.294	35.0	77	0.4560
				38.9	56	59.295	1.719	36.1	91	0.9733

*These units are measured in square meters per ten minutes.

†D.B. = Dry bulb.

‡R.H. = Relative humidity.

high for continuous comfort. They considered the 20.3° C. temperature of the comfortable atmosphere too low for continuous use. Definite chilling would have developed in several hours. A temperature of about 24° or 25° C. would have been more comfortable for continuous use when the relative humidity remained about 50 per cent. Two of the patients were placed in a room with a temperature of 115° C. and 49 per cent relative humidity. This resulted in extreme discomfort with dyspnea, restlessness, and irritability. They were not able to withstand the high temperature long enough for observations of heat and water loss. Because of this experience with two of the subjects, others were not subjected to such hot atmosphere.

PATIENTS WITH RIGHT AND LEFT VENTRICULAR CONGESTIVE HEART FAILURE (FUNCTIONAL QUIETLY IN A WARM ATMOSPHERE)

RATE OF HEAT LOSS								
WATER VAPORIZED		LIBERATION OF CO ₂		WARMING AIR		TOTAL LOSS FROM LUNGS		TOTAL BODY HEAT LOSS
CAL./M. ² /10*	% TOTAL	CAL./M. ² /10*	% TOTAL	CAL./M. ² /10*	% TOTAL	CAL./M. ² /10*	% TOTAL	CAL./M. ² /10*
0.380	5.63	0.247	3.66	0.018	0.27	0.645	9.56	6.75
0.542	7.06	0.275	3.58	0.014	0.18	0.831	10.82	7.68
0.505	5.19	0.351	3.61	+0.033	+0.34	0.856	8.78	9.73
0.677	7.55	0.294	3.28	0.013	0.14	0.984	10.97	8.97
0.522	7.27	0.261	3.64	0.005	0.06	0.788	10.97	7.18
0.708	8.21	0.312	3.62	+0.010	+0.12	1.010	11.72	8.62
0.475	6.49	0.290	3.96	+0.060	+0.08	0.771	10.53	7.32
0.603	5.74	0.387	3.69	0.014	+0.13	0.976	9.30	10.50
0.552	6.64	0.302	3.63	+0.008	+0.002	0.858	10.33	8.34
0.380	5.19	0.247	3.28	-0.018	-0.27	0.645	-8.78	6.75
0.708	8.21	0.387	3.96	+0.060	+0.34	1.010	11.72	10.50
0.105±	0.980±	0.042±	0.720±	0.033±	0.200±	0.115±	0.977±	1.258±
0.026	0.245	0.011	0.180	0.008	0.050	0.029	0.244	0.315
19.02±	14.76±	13.90±	19.83±	112.50±	100±	13.40±	4.58±	15.08±
4.76%	3.69%	3.48%	4.96%	103.13%	25%	3.35%	1.15%	3.77%

PATIENTS WITH RIGHT AND LEFT VENTRICULAR CONGESTIVE HEART FAILURE (FUNCTIONAL IN A FAIRLY WARM ROOM ATMOSPHERE)

RATE OF HEAT LOSS								
WATER VAPORIZED		LIBERATION OF CO ₂		WARMING AIR		TOTAL LOSS FROM LUNGS		TOTAL HEAT LOSS
CAL./M. ² /10*	% TOTAL	CAL./M. ² /10*	% TOTAL	CAL./M. ² /10*	% TOTAL	CAL./M. ² /10*	% TOTAL	CAL./M. ² /10*
0.560	7.14	0.285	3.64	+0.026	+0.33	0.819	10.45	7.84
0.262	3.49	0.272	3.62	+0.019	+0.25	0.515	6.86	7.51
0.514	5.39	0.361	3.79	+0.040	+0.41	0.835	8.76	9.53
0.473	5.39	0.312	3.55	+0.042	+0.48	0.743	8.46	8.78
0.495	5.52	0.344	3.84	+0.051	+0.60	0.788	8.79	8.96
0.461	5.39	0.315	3.69	+0.036	+0.41	0.740	8.66	8.52
0.262	3.49	0.272	3.55	+0.019	+0.0025	0.515	6.86	7.51
0.560	7.14	0.361	3.84	+0.051	+0.0060	0.835	10.45	9.53

DISCUSSION

Fig. 2 illustrates graphically the relationships of the rates of water and heat loss from the respiratory tract in normal subjects and patients suffering with congestive heart failure. The environmental conditions were cool and foggy, comfortable, and warm. It is noted that the rates of both water and heat loss tended to be slightly higher in the patients with heart failure. Detailed comparisons could not be made with the normal subjects for the warm atmosphere since the latter were studied mainly at higher atmospheric temperatures. The relationships were essentially the same, however, as for the lower temperatures in the few instances where comparisons were possible. These findings

are in keeping with results found for other normal subjects and patients with heart failure resting in a comfortable environment.¹

It is also evident from Fig. 2 that a warm environment stimulates the rate of irrigation of the respiratory tract with air. This stimulation is not the result of an increased demand for oxygen to meet metabolic requirements, for the rate of oxygen consumption did not rise under warm environmental conditions. The precise mechanism by which warm environmental air stimulates respiration is unknown. It is possible that there is a psychic element since a hot atmosphere (115° to 120° F.) resulted in marked apprehension and a sense of suffocation.

It was noted in a previous report¹ that the presence of free fluid in the lungs due to the heart failure did not increase the rate of water loss from the lungs. The greater rate of water loss encountered in the patients with heart failure was due to the dyspnea and more rapid irrigation of the respiratory tract with air. Reasons for the failure of greater water loss in the presence of free fluid in the lungs were discussed in the previous report.¹

Although the cool foggy atmosphere was uncomfortable, it did not result in any differences in the rates of water and heat loss from that observed in a comfortable environment. The warm environment did result in a slight change in the rates, especially the rate of ventilation of the lungs. This increase over the normal indicated a detrimental influence on the respiratory tract in the presence of congestive heart failure. When the room air was made hot and humid (120° F. and 49 per cent relative humidity) the patients were not able to remain in the hot atmosphere long enough to complete an observation, because of marked dyspnea and even acute cardiac asthma. The normal subjects were able to remain under such hot and humid environmental conditions for prolonged periods of study without showing respiratory and circulatory embarrassment.

These studies, as well as those previously reported,¹ indicate the need for ensuring a comfortable environment for patients with congestive heart failure. Although a cool and foggy environment does not exert so great a stimulatory influence on the respiratory tract as a warm or hot and moist environment, patients who must lead a quiet existence cannot rest when they are uncomfortably cool. This indicates the need for greater use of air conditioning of hospital wards and rooms of cardiac patients. Likewise, this suggests the value of living in a comfortable balmy climate instead of a cold or hot one while under treatment for congestive heart failure. Patients with anginal failure were not included in these studies.

SUMMARY

Patients with congestive heart failure, Functional Class IV, moderately severe, were studied to learn the influence of variations in the environmental temperature and humidity upon the rates of water and heat loss from the respiratory tract. It was found that these rates were essentially the same for cool and foggy, and comfortable environments. The patients with congestive heart failure did not differ significantly from the normal under those atmospheric conditions. In a warm environment, the rate of irrigation of the respiratory tract

with air was definitely increased; an increase out of proportion of the demands for oxygen. There was also a tendency for a slight increase in the rate of water and heat loss from the respiratory tract.

The patients were unable to stand the very hot and humid atmospheres. Two reacted rather dramatically with dyspnea, apprehension, and even acute cardiac asthma. Because of these reactions, observations could not be satisfactorily conducted.

These studies indicate a greater need for ensuring a comfortable and balmy environment or climate. These patients must be kept quiet physically and therefore are likely to be uncomfortable in a cool climate. A very hot climate or atmosphere is detrimental. There is a need for greater use of air conditioning to ensure atmospheric comfort, especially in hospital rooms and wards where cardiac patients are under treatment.

The author wishes to express an extreme appreciation to Mr. G. Morgavi for his keen interest and important technical assistance in these studies.

REFERENCES

1. Burch, G. E.: The Rates of Water and Heat Loss From the Respiratory Tract of Patients with Congestive Heart Failure Who Were From a Subtropical Climate and Resting in a Comfortable Atmosphere, *AM. HEART J.* 32: 88, 1946.
2. Burch, G. E.: The Influence of Environmental Temperature and Relative Humidity on the Rate of Water Loss Through the Skin in Congestive Heart Failure in a Subtropical Climate, *Am. J. M. Sc.* (In press.)
3. Burch, G. E.: A Study of Water and Heat Loss From the Respiratory Tract of Man. Methods: I. A Gravimetric Method for the Measurement of the Rate of Water Loss. II. A Quantitative Method for the Measurement of the Rate of Heat Loss, *Arch. Int. Med.* (In press.)
4. Nomenclature and Criteria for Diagnosis of Diseases of the Heart by the New York Heart Association, New York, 1942.

THE EFFECT OF MEALS ON THE ELECTROCARDIOGRAM IN NORMAL SUBJECTS

ERNST SIMONSON, M.D., HOWARD ALEXANDER, PH.D.,
AUSTIN HENSCHEL, PH.D., AND ANCEL KEYS, PH.D.
MINNEAPOLIS, MINN.

ANY method as widely used in clinical medicine and applied physiology as the electrocardiogram should be carefully standardized. This means that all conditions and factors which might affect the electrocardiogram should be recognized and considered. In view of the known influence of meals on most circulatory functions, it is surprising that no experimental study on the influence of meals on the electrocardiogram has been reported except a preliminary communication by Gardberg and Olsen.¹ They investigated nine normal young adults before and thirty minutes after an "ordinary mixed meal." Apparently only one experiment was made on each subject. Seven showed a decrease of the T wave in Lead I or III, or in all three standard leads. There was no correlation with the heart rate and no sufficient axis change to explain the change of the T wave. In "several other subjects" it was found that the T-wave changes persisted for two or two and one-half hours.

The authors regarded their material as insufficient to arrive at final conclusions. In this Laboratory, several electrocardiographic studies are in progress concerning the effect of various nutritional states and physiologic stresses. For this reason, we were interested in the standardization of the conditions under which the electrocardiogram is taken. We thought that a special study of the influence of meals on the electrocardiogram would be necessary for the research program here and might have valuable clinical applications, since many cardiac patients complain of distress after meals.

In order to arrive at an exact prediction of normal limits of electrocardiographic changes after food intake, the results were treated mathematically using the usual *t*-test as well as a new procedure based on the analysis of variance.²

METHOD

The basic series consists of 72 experiments on 12 normal subjects* with the three standard leads taken immediately before and thirty minutes after the meal. The electrocardiograms before the meal were taken four to five hours after a

From the Laboratory of Physiological Hygiene, University of Minnesota, Minneapolis, Minn.

The work described in this paper was done, in part, under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Regents of the University of Minnesota. Important assistance was provided by the Sugar Research Foundation, Inc., and the National Dairy Council, Chicago, acting on behalf of the American Dairy Association.

Received for publication Dec. 17, 1945.

*All subjects were volunteers assigned to this Laboratory for Civilian Public Service by the Selective Service System.

light breakfast. The subjects were young men from 19 to 32 years of age. During the period of the experiments and for about six months prior to this series, they were living in this Laboratory under controlled conditions of activity, rest, and nutrition. During this period they were frequently examined with clinical and physiologic methods; no evidence of disease was found in any of our subjects. This was true also for one of our subjects with a borderline left axis deviation.

The test meals varied in composition in the following way: weight, 200 to 269 grams; total calories, 942 to 1,548; carbohydrate calories, 41 to 61 per cent; protein calories, 9.2 to 14.2 per cent; fat calories, 29 to 43 per cent. In another series (II) of 24 experiments on the same 12 subjects, the fat calories of the meals were increased to 82.6 per cent, with a corresponding decrease of carbohydrates to 14.3 and protein to 3.1 per cent, with a total caloric content of 1,437 calories. In a final series (III) of 24 experiments on 8 subjects, three chest leads (CF_1 , CF_2 , and CF_4) were taken in addition to the standard leads; furthermore, the electrocardiograms were taken thirty as well as sixty minutes after the meal. In this series, the same mixed meals were given as in Series I.* The place where the chest leads were taken before the meal was marked with a colored pencil in order to provide accurate reproducibility in the subsequent tracings.

In all three series, the heart sounds were recorded simultaneously with the electrocardiogram during arrested respiration. The following intervals were measured: duration of P wave, duration of the P-R interval, QRS interval, Q-T interval, and duration of the mechanical systole, defined as the interval between the start of the major oscillations of the first heart sound and the beginning of the second heart sound. Both Q-T interval (electrical systole) and mechanical systole were averaged from five beats, usually in Lead II. The constant K was calculated both for Q-T (K_{QT}) and mechanical systole duration (K_{syst}), using the formula $K = \frac{Q-T \text{ or } syst.}{\sqrt{R-R}}$. The average heart rate was calculated from ten beats; in addition, the shortest and longest R-R intervals of the whole record were measured. Their difference was used as a criterion of arrhythmia. The amplitudes of the P wave, the QRS complex, and the T wave were measured in all leads. The QRS axis and the T axis were calculated, using Dieuaide's procedure. Since there was no significant change of the QRS axis, the usual clinical method for estimation of the over-all magnitude of the QRS complex as the sum of the amplitudes in Leads I, II, and III appeared to be sufficient instead of calculation of the hypothetical manifest potential. In Tables I, II, III, and IV the symbol Σ_{QRS} will be used to express this value. A similar procedure was used for the T waves (Σ_T).

Statistical Methods.—For the purpose of testing the statistical significance of the effect of a meal, the *t*-test (Fisher,³ Goulden⁴) was used in all three series. For the data of Series I, consisting of six trials on each of 12 subjects, a more detailed analysis was possible. The values of the difference, $d = \text{value}$

*The meals in all three series were always ordinary warm lunches, but none of the food items was hot nor were strong spices or seasonings employed. Two glasses of liquids were supplied with each meal, a glass of cold water (from the tap) and a glass of cold milk (from an ordinary kitchen refrigerator). Neither coffee nor tea was provided.

after meal minus value before meal, were tabulated in two-way tables (trials versus individuals), and the usual methods of analysis of variance (Fisher, Goulden) were applied in order to break down the total variation into its components as shown in the following:

SOURCE OF VARIATION	MEAN SQUARE	DEGREES OF FREEDOM
Effect of the meal	V_m	1
Individuals	V_i	11
Trials	V_t	5
Interaction of residual	V_{it}	55
		<hr/> 72

The term V_m is not usually included in such a breakdown, since it is merely equivalent to $72 \bar{d}^2$, where \bar{d} is the mean value of d . If we combine the last three items (V_i , V_t , and V_{it}) we obtain the "total" mean square, V_i with 71 degrees of freedom (df). The t -test referred to earlier is equivalent to the F -test: $F = V_m/V_i$, which is simply the square of the value of t . But these equivalent tests are not valid unless it has been shown that only a single source of variation is present, that is, when neither $F = V_i/V_{it}$ nor $F = V_i/V_t$ is significant. As this is virtually never the case with such data as those at hand, a more suitable test must be used.

The validity of the test which was developed rests upon a basic assumption. We assume that the difference d for individual h on trial k (which may be designated d_{hk}) can be expressed as the sum of four components due, respectively, to the effect of a meal, to the variation between individuals, to trials, and to interaction: $d_{hk} = M + I_h + T_k + R_{hk}$; and that each of the terms on the right is normally distributed, with population variances σ_m^2 , σ_i^2 , σ_t^2 , and σ_{it}^2 . If we denote by s_m^2 , s_i^2 , s_t^2 , and s_{it}^2 unbiased estimates¹ derived from the sample of the corresponding population variances, then we have the equations:

$$\begin{aligned} V_m &= 72s_m^2 + 6s_i^2 + 12s_t^2 + s_{it}^2 \\ V_i &= 6s_i^2 + s_{it}^2 \\ V_t &= 12s_t^2 + s_{it}^2 \\ V_{it} &= s_{it}^2 \end{aligned}$$

These equations may be solved for s_m^2 , s_i^2 , s_t^2 , and s_{it}^2 .

Wilson² has suggested two tests, designated F' and F'' , to replace the F -test in the present situation. F' and F'' are defined by:

$$\begin{aligned} F' &= V'_m/V_i, & V'_m &= V_m - V_t + V_{it} = 72s_m^2 + 6s_i^2 + s_{it}^2; \\ F'' &= V''_m/V_t, & V''_m &= V_m - V_i + V_{it} = 72s_m^2 + 12s_t^2 + s_{it}^2. \end{aligned}$$

These are the tests that have been used on the present data. F' is a test of whether the total variability is attributable to the joint action of individual and residual variability, and F'' is a test of whether the total variability is attributable to the joint action of trial and residual variability. These tests will be further discussed by Alexander in a separate communication.²

TABLE I. MEAN VALUES, DIFFERENCES, VARIABILITY, AND RANGE OF LEAST SIGNIFICANT DIFFERENCES OF SEVERAL ELECTROCARDIOGRAPHIC FUNCTIONS BEFORE AND AFTER A MEAL

ELECTROCARDIOGRAPHIC FUNCTION	MEAN VALUES		DIFFERENCES	TOTAL VARIABILITY	LEAST SIGNIFICANT DIFFERENCES			RANGE OF LEAST SIGNIFICANT DIFFERENCES				GROUP	
	BEFORE	AFTER			5%	1%		-	TO	+	TO		+
P-wave amplitude, Lead II	0.08	0.09	+0.01	0.02	0.06	0.08	0.06	0.06	0.07	0.08	0.09	B	
K _{sys}	0.32	0.32	0.00	0.01	0.03	0.03	0.02	0.02	0.03	0.03	0.03		
Heart rate range	6.18	6.72	+0.54	4.21	8.49	11.24	7.95	7.95	9.03	10.70	11.78		
QRS axis (°)	54.24	54.26	+0.03	5.76	11.61	15.38	11.58	11.58	11.64	15.35	15.41		
Σ QRS (mv.)	2.81	2.98	+0.17	0.45	0.90	1.20	0.73	0.73	1.07	1.03	1.37	C	
R-wave, Lead II	1.14	1.21	+0.07	0.18	0.37	0.49	0.30	0.30	0.43	0.42	0.55		
T axis (°)	45.46	40.03	-5.43	12.51	25.19	33.37	30.62	30.62	19.76	38.80	27.94		
Average heart rate	53.44	60.60	+7.16	4.67	9.40	12.45	2.25	2.25	16.55	5.30	19.60	D	
Systole duration, 0.01 second	34.11	32.17	-1.94	1.76	3.55	4.70	5.49	5.49	1.60	6.64	2.76		
Q-T, 0.01 second	38.78	37.10	-1.68	1.51	3.05	4.04	4.73	4.73	1.37	5.72	2.36		
K _{qr}	0.36	0.37	+0.01	0.01	0.03	0.03	0.02	0.02	0.03	0.03	0.04		
T, Lead I (mv.)	0.29	0.22	-0.07	0.06	0.11	0.15	0.18	0.18	0.48	0.21	0.08		
T, Lead II (mv.)	0.39	0.26	-0.13	0.08	0.16	0.21	0.29	0.29	0.03	0.34	0.08		
Σ T	0.82	0.59	-0.23	0.15	0.31	0.40	0.54	0.54	0.07	0.64	0.02		
T, Lead CF ₁ (mv.)	-0.16	-0.07	-0.09	0.35	0.74	1.00	0.65	0.65	0.83	0.91	1.09		
T, Lead CF ₂ (mv.)	0.73	0.66	-0.07	0.18	0.27	0.36	0.34	0.34	0.19	0.43	0.29		
T, Lead CF ₃ (mv.)	0.95	0.71	-0.24	0.13	0.27	0.37	0.51	0.51	0.04	0.61	0.13		

RESULTS

The various functions of the electrocardiogram did not respond in the same way to a meal. From the standpoint of statistical evaluation, the functions may be subdivided into four groups.

Group A.—This group consists of comparatively stable functions which show only minor changes, hardly exceeding the technical error of measurement. These functions are: duration of P, P-R interval, QRS interval, Q wave and S-T segment. No tables are given for these functions.

Group B.—This group consists of functions with fairly frequent but not statistically significant changes. This group includes P amplitude in Lead II, QRS axis, range of heart rate, and K_{sys} . The mean values are given in Table I, and the values of t , F' and F'' are given in Table II. Neither the t -test, nor the F' and F'' tests are significant for these functions.

TABLE II. STATISTICAL SIGNIFICANCE OF ELECTROCARDIOGRAPHIC CHANGES AFTER THE MEAL.

TEST	$F = V_m/V_t$	$F' = V_m'/V_t$	$F'' = V_m''/V_t$	GROUP
Significance:				
for 5% level	3.98	1.84	6.61	
for 1% level	7.00	9.65	16.26	
Electrocardiographic functions:				
K_{sys}	0.14	1.139	1.606	B (not significant)
P wave, Lead II	0.57	0.906	0.737	
QRS axis	1.92	0.431	0.256	
	0.002	0.142	4.924	
R, Lead II	9.94	7.998	2.595	C (significant with F test)
Σ QRS	10.79	7.760	1.991	
T axis	14.06	3.816	51.608	
Average heart rate	176.79	51.120	115.570	D (significant with all tests)
Systole duration	88.75	43.246	150.136	
QT interval	67.59	20.357	79.684	
K_{QT}	25.631	15.367	17.442	
T, Lead I	98.83	44.75	50.093	
T, Lead II	199.91	73.798	72.178	
Σ T	181.65	57.940	66.280	
$\log \Sigma T$	161.74	126.30	35.03	

Group C.—This group consists of functions with consistent changes, significant according to the t -test but not according to the more refined F' and F'' tests. In this group we find the T axis, and the QRS and R-wave amplitude in Lead II. The mean values of these functions are given in Table I, and the tests of significance are given in Table II.

Group D.—This group consists of functions whose changes are highly significant according to the t -test and also according to the F' and F'' tests. In this group are average heart rate, absolute value of Q-T interval, K calculated for Q-T, absolute mechanical systole duration, T amplitude in Leads I and II, and ΣT . Although not listed in the tables, the significance of the change in the T wave in Lead III is implied by the high significance of the T-wave changes in Leads I and II, and ΣT . Mean values for these functions are listed in Table I and the tests of significance are given in Table II.

In Table I there are also shown, for the functions of Group D, the total variability, the least significant differences due to the effect of a meal at the

5 per cent and 1 per cent levels, and the range of least significant differences. The total variability σ_d^2 is defined by $\sigma_d^2 = \sigma_1^2 + \sigma_t^2 + \sigma_{it}^2$, where σ_1 , σ_t , and σ_{it} are the population variances. σ_d^2 is thus the total variance of the difference d , the combined effect of the several sources of variation. The least significant differences (LSD) are defined by $\text{LSD} = \sigma_d \times t$, where t is the 5 per cent or the 1 per cent value of t with 71 *df*. Finally, the least significant range is defined by (Mean - LSD) to (Mean + LSD). At the 5 per cent level, this gives the range within which 90 per cent of the obtained values of d may be expected to lie; similarly, 98 per cent of the obtained values of d may be expected to lie within the 1 per cent least significant range. Values exceeding these ranges may be judged abnormal, in comparison with our group or normal young men.

Heart Rate.—The average heart rate increased by 7.1 beats per minute after the meal, with a total variability of ± 4.67 (Table I). This increase was highly significant (Table II). On the other hand, there was no significant increase of the range of the heart rate, calculated from the difference between the shortest and longest R-R interval (Table I). Therefore, there is no increased tendency to sinus arrhythmia associated with the increased heart rate. It will be noted that the heart rate before the meal indicates sinus bradycardia in the majority of our subjects. According to the experience of this Laboratory, sinus bradycardia is rather common among normal young men.

Duration of Mechanical Systole, Q-T Interval, K_{syst} , and K_{QT} .—With the shortening of the R-R interval after the meal, a shortening of both the duration of the mechanical (syst) and of the electrical systole (Q-T) should be expected. This is indeed the case, as can be seen in Table I. The values are given in hundredths of a second. The difference is small, but statistically highly significant (Table II). The constant K would express whether the shortening of mechanical (syst) and electrical (Q-T) systole would conform to the shortening of the R-R interval in a proportion as indicated by the formula, or whether the change of Q-T or mechanical systole (syst) is out of the normal proportion. In the first case, K would remain the same; in the second case, K would change. Tables I and II show that there is a highly significant increase of K_{QT} . This means that the Q-T interval, although significantly shorter after the meal, does not shorten quite in proportion to the decrease of the R-R interval. After the meal, the Q-T interval is relatively larger than it was before the meal. In contrast, there is no statistically significant change of K_{syst} ; in fact, the difference of the means is zero (Table I). However, this does not mean that K_{syst} belongs to the Group A of stable functions. K_{syst} remained the same within ± 0.002 in only 10 of 72 experiments; the changes exceeded ± 0.01 in 25 experiments. Occasionally, rather large changes were observed up to +0.032 and -0.024. The changes occurred in both directions and were erratic both in regard to individual and trial variability. The different response of K_{syst} and K_{QT} is not surprising. Discrepancies in the response of K_{syst} and K_{QT} have been repeatedly observed under various experimental conditions.^{7, 8}

Duration of P Wave.—The duration of the P wave is essentially the same before and after the meal.

P-R Interval.—There were no changes of the P-R interval in 33 of 72 experiments. In one subject, the P-R interval was consistently shortened (by 0.02 second) after the meal, while in the other subjects the changes were minor or not uniform.

QRS Interval.—The QRS interval was the same (within ± 0.01 second) before and after the meal. The QRS interval appears to be the most stable of all electrocardiographic functions.

P-Wave Amplitude.—There were no changes in the amplitude of the P-waves in Lead I. In Lead II, changes averaging between 0.02 and 0.03 mv. in both directions (increase or decrease) were observed in 49 of 72 experiments. An increase of the P wave (in one experiment by 0.1 mv.) was more common than a decrease, especially when the P wave was small before the meal. The changes were not statistically significant (Table II). In Lead III, the changes of the P wave were similar to those in Lead II. If the P wave was negative or diphasic before the meal, there was a tendency toward greater positivity after the meals.

Q Wave.—In electrocardiograms without a Q wave before the meal, no Q wave appeared after the meal. In electrocardiograms with a small Q wave before the meal, there was a tendency to a slight increase (not exceeding 0.05 mv.) of the Q wave in all leads. Even so, the Q wave remained small and insignificant. Thus, the Q wave may be regarded as a comparatively stable function (Group A).

R-Wave Amplitude in Lead II and Σ_{QRS} .—The R wave in Lead II was increased in 52 and decreased in 15 experiments. In several experiments, the changes, especially increases, were quite considerable (between 0.3 and 0.5 mv.). Due to a larger degree of variability, the average increase was slight (Table I) and significant only for the F-test (Table II).

The distribution of changes of Σ_{QRS} was similar to those of R_2 (55 increases, 15 decreases). The average increase of 0.17 mv. was highly significant for the F-test, and was also significant for the F' test (individual variability), but was not significant for the F'' test (trial variability) (Table II).

No calculations of statistical significance were made for the S wave, since changes of the S wave would be reflected in both Σ_{QRS} and QRS-axis changes.

QRS Axis.—The QRS axis remained unchanged (between $\pm 2^\circ$) in 33 of 72 experiments. In the other 39 experiments there was about an equal incidence of a greater right or left axis shift after the meal. Consequently, the average electrical axis was about the same before and after the meal (Table I). In one subject with left axis deviation before the meal, there was a consistent shift toward the right, so that the left axis deviation was less pronounced. Only minor changes were observed in three subjects with an axis between 75° and 89° , but the same was true also for another subject with an initial axis between 15° and 21° . No consistent relationship between axis change and initial axis was seen in this series.

S-T Segment.—The S-T segment showed only minor changes after the meal with a tendency toward depression, although several slight increases were observed, too. The depression did not exceed -0.06 mv. in Lead III, while the S-T

segment remained positive or isoelectric in Leads I and II. The S-T segment belongs in Group A of comparatively stable functions.

T-Wave Amplitude and Direction.—The most pronounced and consistent changes occurred in the T wave. The T-wave amplitude in Leads I and II, Σ_T , and the electrical axis were analyzed. A decrease of the T wave, in at least one of the limb leads, and usually in all three leads, occurred in all experiments. The decrease of the T-wave amplitude in Leads I, and II, and Σ_T was highly significant for all statistical tests used (Table II). The absolute as well as the percentage difference increased in the above order. It can be inferred that there is also a significant decrease of T_3 . In five subjects with a small positive T_3 before the meal, T_3 became small and diphasic after the meal. In order to decide whether the T-wave changes should be expressed as percentages of the initial T waves rather than in absolute differences, the calculations of statistical significance were made for the logarithms of Σ_T . It can be seen from Table II that the use of logarithms (or percentages) would have no particular advantage.

T Axis.—Of 72 experiments, a shift exceeding 2° toward the left was observed in 40 experiments, and a shift toward the right was seen in 16 experiments. Three subjects showed a consistent shift toward the left in all experiments. The average shift of -5.4° was highly significant for the $F(t)$ -test and trial variability (F''), but not significant for individual variability (F'). There was no correlation between the initial T axis and the shift of the T axis after the meal.

Electrocardiographic Changes After a High-Fat Meal (Series II).—The effect of a meal with 82 per cent fat content was investigated in a total of 24 experiments on 12 subjects. Since only two experiments were available in each subject, only the t -test was calculated. Table III shows the results on some electrocardiographic functions. All electrocardiographic functions which were found to be stable after mixed meals (Group A) were also stable after the high-fat meal, and all functions which showed significant changes in Series I (heart rate, T wave, absolute length of Q-T and mechanical systole, K_{Q-T}), showed similar significant changes also in this series. Most of the functions with frequent, but statistically not significant changes after mixed meals (Group B) showed a similar response after the high-fat meal. This is also true for Σ_{QRS} .

TABLE III. ELECTROCARDIOGRAPHIC CHANGES AFTER A MEAL WITH HIGH-FAT CONTENT (TWENTY-FOUR EXPERIMENTS ON TWELVE SUBJECTS)

ELECTROCARDIO- GRAPHIC FUNCTION	MEAN DIFFERENCE BEFORE AND AFTER MEAL	t	P*	SIGNIFICANCE
Heart rate	+5.96 beats per minute	5.997	0.001	High
K_{QT}	+0.0124	3.77	0.001	High
K_{syst}	+0.0057	1.75	7.05	None
Σ_{QRS}	+0.193 mv.	5.188	0.09	High
QRS axis	-2.21°	1.92	0.05	None
ΣT	-0.171 mv.	7.032	0.001	High
T axis	-4.54°	2.80	0.01	High

*P shows the level of significance expressed as percentage of expected differences; P = 0.01 means that there is only a 1 per cent chance that the difference is due to random variation.

and T axis which showed significant changes in Series I only with the *t*-test. There was a more pronounced tendency to left axis deviation, which was, however, not statistically significant. Taken all in all, the electrocardiographic changes after a meal with a high-fat content are about the same as those after mixed meals.

Electrocardiographic Changes (Including Chest Leads) Thirty and Sixty Minutes After the Meal (Series III).—In order to determine the trend of changes after the meal, in another series (III) the standard leads as well as CF_1 , CF_2 , and CF_4 were taken thirty and sixty minutes after the meal. A total of 24 experiments were performed on eight subjects. However, the trials were not evenly distributed; four repetitions were made in four subjects and two repetitions were made in another four subjects. For this reason, only the *t*-test of significance was used.

Since the meals as well as the subjects were the same as those in Series I, this series may be regarded as a repetition of Series I so far as the thirty-minute interval after the meal is concerned. Thus, Series III affords an opportunity to check the reliability of the predicted range of least significant differences for the 5 per cent and 1 per cent levels (Table I). We compared the mean values and the standard deviations of the group as well as the 24 individual experiments. There was no significant group difference in any electrocardiographic function between Series I and Series III. In regard to the individual experiments, all values of all electrocardiographic functions were within the 5 per cent range of least significant differences except one value of the heart rate which was within the 1 per cent range. Thus, the results of both series are in complete agreement.

There were only minor differences of the various electrocardiographic functions when these functions were compared at the intervals of thirty and sixty minutes after the meal. Sometimes the changes were somewhat more pronounced after sixty minutes; in other cases, they were slightly less pronounced or the same at thirty and sixty minutes. This was true for the limb leads as well as the chest leads (Figs. 1 and 2). In no experiment had the electrocardiographic changes disappeared within sixty minutes. Table IV shows that the mean differences of several electrocardiographic functions of Group D are about the same thirty and sixty minutes after the meal. No function showed statistically significant differences between thirty and sixty minutes. This is

TABLE IV. MEAN DIFFERENCE OF SEVERAL ELECTROCARDIOGRAPHIC FUNCTIONS THIRTY AND SIXTY MINUTES AFTER THE MEAL

FUNCTION	30 MIN.	60 MIN.
Average heart rate	+6.54	+7.50
Mechanical systole duration 0.01 second	-1.87	-2.17
QT interval, 0.01 second	-0.96	-1.12
Σ QRS (mv.)	+0.30	+0.25
QRS axis (degrees)	+1.17°	+1.29°
Σ T (mv.)	-0.19	-0.20
T axis (degrees)	-5.62	-5.33
T, CF_1 (mv.)	+0.09	+0.06
T, CF_2 (mv.)	-0.07	-0.09
T, CF_4 (mv.)	-0.24	-0.26

also true for the individual experiments. Within the 1 per cent range of least significant differences, there was only one value of the heart rate, one value of the duration of mechanical systole, one value of the Q-T interval, and two values of ΣT in one subject. All other values were within the 5 per cent range. Obviously, the range of least significant differences, predicted from experiments thirty minutes after the meal, is essentially correct also for an interval of sixty minutes after the meal.

The R and S waves of the chest leads CF_1 , CF_2 , and CF_4 showed frequent, but not uniform changes. No Q waves appeared after the meal when these waves were absent before the meal. A small Q wave in CF_4 in one subject

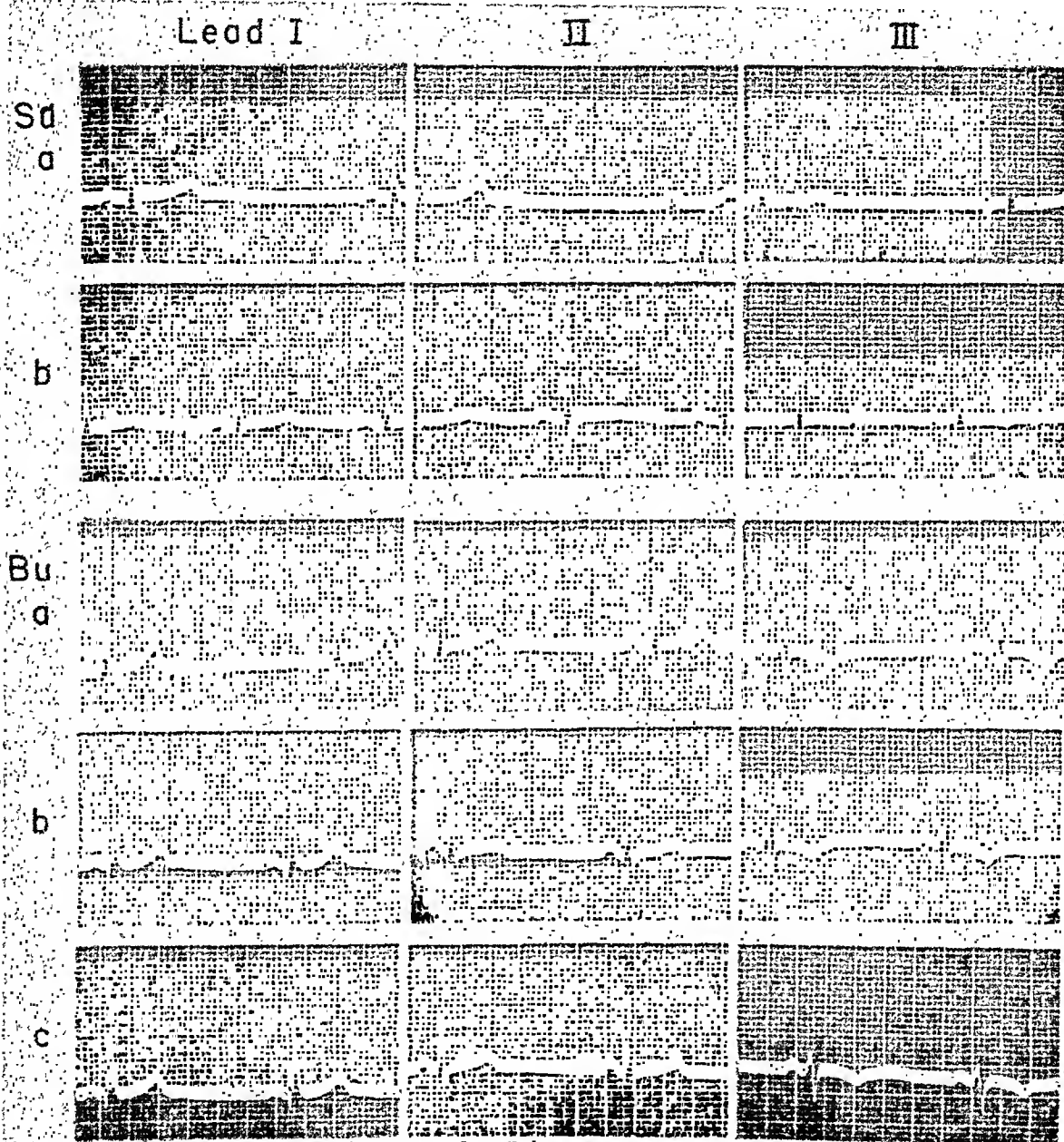


Fig. 1.—Three standard leads before (a), thirty minutes after (b), and sixty minutes after (c) the meal in two subjects (Sa and Bu). Both subjects show a marked decrease of the T wave in Leads I and II after the meal; in subject Bu, this was more pronounced at thirty than at sixty minutes after the meal. In subject Sa the positive T wave in Lead III becomes small and diphasic after the meal. No significant axis shift can be seen. The slightly elevated S-T segment in Lead I of subject Bu is seen to be still elevated after the meal. Subject Sa has a small diphasic P_2 (not common in normal people), which is larger and positive after the meal. A similar change occurs in P_2 .

remained the same after the meal. The changes of the T waves were highly significant. In CF_1 , there was a shift toward greater positivity, i.e., the negative or diphasic T wave became less inverted or positive (Fig. 2). In CF_2 and CF_4 , the T wave became smaller, more so in CF_4 than in CF_2 . The values, differences, variability, and range of least significant differences are given in

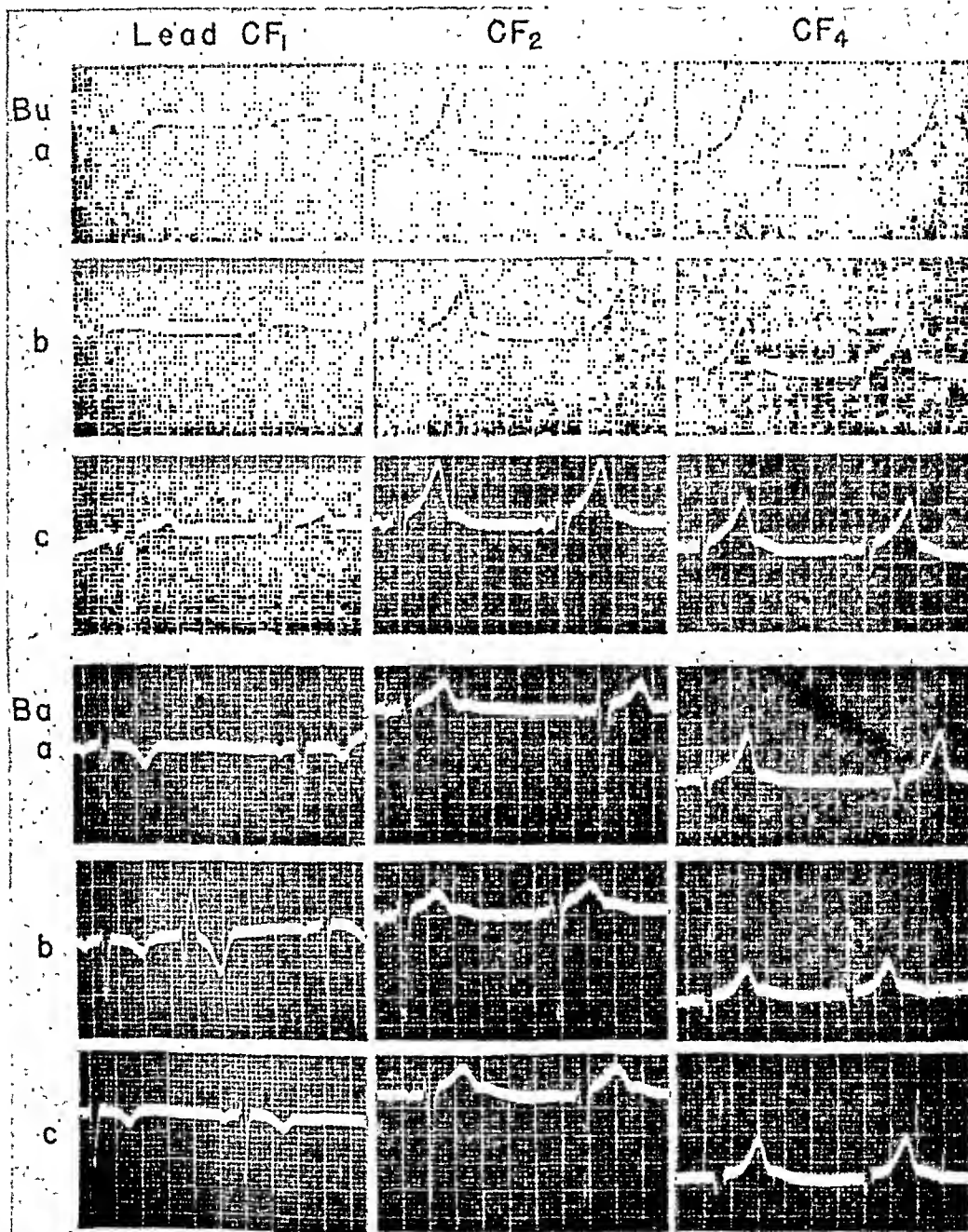


Fig. 2.—Three chest leads (CF_1 , CF_2 , and CF_4) before (a), thirty minutes after (b), and sixty minutes after (c) the meal in two subjects (Bu and Ba). In Lead CF_1 , the diphasic T wave of subject Bu before the meal becomes progressively positive after the meal; the T wave of subject Ba is less inverted after the meal. In both subjects the T wave decreases after the meal in Leads CF_2 and CF_4 .

Table I. Changes of the S-T segment were minor with a tendency to slight elevation in CF_1 and an opposite tendency to slight depression in CF_4 , but in no case was this segment deviated below the isoelectric line.

COMMENT

The experiments show that consistent changes of various fundamental electrocardiographic functions appear after the intake of moderate meals. Thus, food intake should be considered as a major factor in the standardization of the electrocardiographic procedure. The changes are present at least sixty minutes after the meal, and probably, according to Gardberg, and Olsen,¹ for two or two and one-half hours. The changes might be more pronounced or more prolonged after heavy meals, although changes within the range of our diets showed no significant differences.

In no case did the electrocardiogram become abnormal after the meal. It might appear that food intake is of little consequence for the normal electrocardiogram in regard to clinical diagnosis. However, this might not be true for borderline or abnormal electrocardiograms. Experiments on this question are in progress.

The most important effect of the meal is the decrease of the T wave. There was no correlation between the changes of heart rate, QRS axis, or QRS amplitude. Probably the decrease of the T wave might be explained as due to sympathetic stimulation, as has been suggested for the decrease of the T wave in adjustment tests to vertical position.⁹ A reduction of the coronary blood flow is not likely to be responsible for the T-wave changes in normal young persons, since they were not associated with changes of the S-T segment.

SUMMARY

1. The effect of meals on the electrocardiographic pattern was studied in 120 experiments on 12 normal young men.

2. The electrocardiograms were taken before, thirty minutes after, and, in some cases, sixty minutes after standard mixed meals and high-fat content meals of 942 to 1,548 calories.

3. The three standard limb leads were taken in all 120 experiments, and in 24 experiments chest leads CF_1 , CF_2 , and CF_4 were also taken. The results were analyzed by precise statistical methods.

4. In the limb leads the significant changes observed were an increase of heart rate, increase of K_{QT} (i.e., $QT/\sqrt{R-R}$); a decrease of the T wave, a decrease of the duration of mechanical systole, a decrease of the Q-T interval, an increase of the QRS amplitude, and a left axis shift of the T axis.

5. Frequent but not consistent changes were observed in the P wave, range of heart rate, and K, calculated from the duration of mechanical systole.

6. The P-R and QRS intervals, the Q-wave, and the S-T segment showed little change.

7. The T wave in CF_1 became more positive; in CF_2 and especially in CF_4 , the T wave was decreased.

8. The changes produced by the standard mixed meals and the high-fat meals were similar.

9. The changes observed at thirty minutes after a meal were present with only minor variations at sixty minutes after a meal.

10. Some practical applications to electrocardiographic procedure are discussed.

REFERENCES

1. Gardberg, M., and Olsen, F.: Electrocardiographic Changes Induced by the Taking of Food, *AM. HEART J.* 17: 725, 1933.
2. Alexander, H.: Analysis of Variance in Experimental Human Biology. In preparation.
3. Fisher, R. A.: Statistical Methods for Research Workers, Edinburgh, 1936.
4. Goulden, C. H.: Methods of Statistical Analysis, New York, 1939, John Wiley & Sons, Inc., p. 135.
5. Kenney, J. F.: Mathematics of Statistics, Part 2, New York, 1939, D. Van Nostrand Company, Inc.
6. Wilson, H. G.: Notes on Analysis of Experiments Replicated in Time, *Biometrics Bull.* 1: 16-20, 1945.
7. Barto, E., and Bunstein, J.: Can Variations in Ventricular Systole Be Determined From Electrocardiogram Deflections? *J. Lab. & Clin. Med.* 9: 217, 1924.
8. Barker, P. J., Johnston, F. D., and Wilson, F. N.: The Duration of Systole in Hypocalcemia, *AM. HEART J.* 14: 82, 1937.
9. Meyerson, H. S., and Davis, W. D.: The Influence of Posture on the Electrocardiogram, *AM. HEART J.* 24: 593, 1942.

THE VELOCITY OF BLOOD FLOW IN NORMAL PREGNANT WOMEN

BENJAMIN MANCHESTER, M.D., F.A.C.P., AND SAMUEL D. LOUBE, M.D.
WASHINGTON, D. C.

IN 1928, Blumgart and Weiss¹ demonstrated the clinical value of measuring the velocity of blood flow in health and disease. This has since become an accepted procedure in the careful evaluation of an individual's cardiac reserve. The ability to recognize early heart failure by measuring the velocity of blood flow has now been clearly established. In isolated left ventricular failure, when the physical signs may be meager, the only evidence of its presence may be a prolonged arm-to-tongue and lung-to-tongue time. In like manner, it is possible to recognize the imminence or presence of right heart failure by the prolonged arm-to-tongue and arm-to-lung time, even before the venous pressure is elevated.

The difficulty in recognizing early heart failure in pregnant women, especially when decompensation occurs in the last trimester, is fully appreciated by all who have had any experience with this problem. The measurement of the velocity of blood flow as a means of detecting early heart failure in pregnancy has been attempted, but with equivocal results. This has been due to the fact that the range of normal circulation time in pregnancy has not been established.

The value for the arm-to-tongue time of normal adults is 9 to 16 seconds when calcium gluconate, saccharin, magnesium sulfate, or decholin is employed. That for the arm-to-lung time is 4 to 8 seconds, using ether and/or paraldehyde. There is no evidence that this accepted range applies to the normal pregnant woman.

A search of the literature discloses that there is no unanimity of opinion as to whether the velocity of blood flow in the course of normal gestation is increased, decreased, or the same as in the nongravid woman. In 1924, Klee² measured the blood flow during pregnancy by the fluorescein method of Koch.³ He found that the circulation time was prolonged to 25.2 seconds in primiparas and to 23.4 seconds in multiparas (the normal time being 20 seconds). The greatest slowing of blood flow occurred in the eighth month. Only a single observation was made on each of 100 women in the final trimester of pregnancy. Spitzer,⁴ employing decholin and a single determination, found the velocity of blood flow to be the same in the pregnant and nonpregnant states. In a study reported by Cohen and Thomson,⁵ 100 determinations, using the cyanide method of Robb and Weiss,⁶ were made on 37 pregnant women. The average velocity of blood flow was normal in the first trimester of pregnancy (9 to 21

From Garfield Memorial Hospital, and the Department of Medicine, George Washington University School of Medicine, Washington, D. C.

Received for publication Dec. 17, 1945.

seconds), increased in the second trimester of gestation beginning with the seventeenth week, and remained increased until the thirty-fifth week, when it again decreased just prior to term. Landt and Benjamin⁷ employed decholin in 19 cases and found the velocity of blood flow to be the same in the pregnant as in the nonpregnant state. Using the saccharin method in 13 normal pregnant women, Greenstein and Clahr⁸ found that the circulation time increased from the eighteenth to the thirty-eighth week, and decreased in the fortieth week. The apparent discrepancy in these results prompted the present study.

The purpose of this investigation was to determine the velocity of blood flow in pregnant patients without heart disease: the range of normal, from the first trimester until the conclusion of gestation.

METHOD AND MATERIALS

A total of 48 women were examined near the beginning of pregnancy. A complete history and physical examination were made with the purpose of excluding any individual with heart disease. In a few cases, basal metabolism and blood cholesterol determinations were made in order to exclude patients with hyperthyroidism. Of this original group, all 48 were followed until the completion of gestation.

The patients' weight, temperature, pulse, and respirations were recorded at each examination. Anyone with a temperature above 99° F. and/or a pulse above 120 was not examined on that day, but was asked to return on a subsequent day. Each patient was made to rest in the recumbent position for ten minutes prior to the determination. The ante-cubital vein was selected as the site of venipuncture, the same arm being used wherever possible. Ten cubic centimeters of 20 per cent calcium gluconate was used for the arm-to-tongue time determination, and 0.5 c.c. of a 50 per cent solution of paraldehyde in ether was used for the arm-to-lung time measurement. The circulation time was measured by a stop watch. The skin overlying the site was anesthetized with 1 per cent novocain to allay anxiety and fear of the venipuncture. The same observer always performed the same test on the same patient. During the first few visits the patient was informed of the end points for both measurements and reassured. Only 18- or 19-gauge needles were used.

The test was performed in the following manner: With the tourniquet about the arm, venipuncture was made into the anesthetized skin. The arm was abducted to a 90-degree angle, the tourniquet was released, and no injection was started until the venous congestion in the arm had abated. A stop watch was released, and when the second hand reached the five-second mark, the 5 c.c. of the 20 per cent calcium gluconate were injected rapidly (total injection requiring one to two seconds). Upon the perception of sensation of warmth in the tongue or mouth, the patient indicated by saying "Now," and the time was then recorded by the stop watch, after five seconds were subtracted from the total time. After the sensation of heat had subsided, the arm-to-tongue time determination was repeated with the additional 5 c.c. of solution. This was done to check on the reliability of the subjective response. An average of the two determinations was taken as the final result. In cases

where the difference was greater than three seconds, the results were discarded, and the patient was requested to return on a subsequent day.

After the measurement of the arm-to-tongue time had been made, the syringe was quickly detached, and the 2 c.c. syringe containing 0.5 c.c. of ether-paraldehyde was applied to the needle in situ. The stop watch was released, and, again at the five-second mark, the solution was injected quickly (requiring less than one-half second for its completion). The end point was usually objective, and was manifested as a short paroxysm of coughing, facial grimaces, and/or simultaneous perception of the paraldehyde-ether odor by the patient and the examiner. The result was then recorded as the arm-to-lung time.

The lung-to-tongue time was obtained by subtracting the arm-to-lung time from the mean arm-to-tongue time.

In this manner, the velocity of blood flow from arm-to-tongue and arm-to-lung was measured every two weeks from early in gestation until term. Of the 73 cases, 48 are available for study and constitute the basis for our observations and conclusions. The remaining 25 cases were discarded because of irregular attendance.

Of the 48 patients studied, 13 were between the ages of 16 and 20 years, 31 were between 21 and 30, and four were 31 or older, the oldest being 37 years old. A total of 712 determinations of both arm-to-tongue and arm-to-lung time were made on the 48 cases studied. In the first, second, and third trimesters, 132, 295, and 285 observations were made, respectively. Ten of the patients were not examined in the first trimester. In eight cases of the remainder, only a single determination was made in the first trimester, and these were not used in computing the final averages.

In the total series, there were eleven cases with unpleasant or untoward reactions. Seven complained of pain along the course of the vein when the paraldehyde-ether mixture was injected. This could always be relieved by the rapid instillation of physiologic saline solution. In most of the cases the pain had subsided before this measure was applied. Two patients had cellulitis at the site of the injection; this was self-limiting and responded to the usual local measures. Two had a short but severe paroxysm of coughing, and two experienced syncope. It was observed that these reactions did not occur in the same individuals on subsequent examinations.

RESULTS

At the conclusion of this study, an evaluation of the results showed that the range of the velocity of blood flow varied with the trimester of gestation. The average circulation times for each patient are recorded in Table I. In the first trimester, the average circulation time from arm-to-tongue ranged from 10.3 to 15 seconds; the average was 12.4 seconds. The arm-to-lung time ranged from 3.8 to 8.3 seconds; the average was 6.6 seconds. In the following three months, the arm-to-tongue time was 9.2 to 15.4 seconds, averaging 11.3 seconds. The arm-to-lung time ranged from 3.8 to 7.7 seconds; the mean was 5.8 sec-

TABLE I. AVERAGE CIRCULATION TIME FOR EACH PATIENT* IN EACH TRIMESTER OF PREGNANCY

PATIENT	AGE (YRS.)	GRAVIDA	FIRST TRIMESTER			SECOND TRIMESTER			THIRD TRIMESTER		
			A-T	A-L	L-T	A-T	A-L	L-T	A-T	A-L	L-T
E. C.	16	I	11.0	5.3	5.7	10.0	5.0	5.0	9.3	4.2	5.1
R. S.	16	I				9.9	5.0	4.9	9.0	4.2	4.8
B. M.	17	I	13.8	7.3	6.5	11.5	6.3	5.2	11.2	6.2	5.0
B. C.	17	I	11.4	6.4	5.0	10.0	4.3	5.7	9.0	4.2	4.8
D. W.	17	I	12.5	6.5	5.0	12.4	7.1	5.3	11.0	6.6	5.0
E. W.	17	II	13.4	7.0	6.4	12.3	7.1	5.2	12.0	6.5	5.5
D. S.	18	I	12.0	6.3	5.7	10.3	4.8	5.5	9.7	4.5	5.2
I. B.	18	I				12.0	7.6	4.4	9.3	4.9	4.4
E. H.	18	I	12.6	7.2	5.4	10.2	5.2	5.0	9.0	4.2	4.8
T. C.	19	I	11.0	3.8	7.2	9.7	4.0	5.7	8.6	3.8	4.8
R. S.	20	II				15.4	7.0	8.4	11.3	6.4	4.9
L. A.	20	I	(13.0)	(7.0)	(6.0)	13.4	6.4	7.0	9.8	5.2	4.6
J. C.	20	III				9.5	4.5	5.0	10.5	5.1	5.4
M. D.	21	II	(13.0)	(8.0)	(5.0)	10.3	5.4	4.9	9.0	5.0	4.9
E. H.	21	III	13.9	7.4	6.5	12.0	6.5	5.5	11.6	6.0	5.6
W. H. G.	22	VII	11.8	6.0	5.8	10.9	5.7	5.2	10.0	4.0	6.0
M. A. W.	22	II	12.8	6.5	6.3	10.7	5.9	4.8	10.2	5.0	5.2
E. S.	23	I	11.3	6.3	5.0	10.2	5.3	4.9	9.8	5.0	4.8
D. B.	23	I	14.0	7.0	7.0	14.0	7.6	6.4	16.2	5.9	10.3
M. C.	23	I	12.3	8.3	4.0	9.3	4.3	5.0	8.8	4.0	4.8
I. J.	23	III	15.0	7.0	8.0	12.8	6.3	6.5	12.2	6.0	6.2
W. M.	23	I	13.6	7.1	6.5	12.2	6.0	6.2	11.1	6.2	5.2
M. T.	23	III				13.5	7.7	5.8	10.8	6.2	4.6
E. B.	24	II	12.0	4.5	7.5	12.6	6.1	6.5	10.8	5.2	5.6
M. M.	24	I	13.2	7.0	6.2	12.2	6.2	6.0	10.8	5.0	5.8
M. D.	24	I	15.0	8.0	7.0	12.8	6.7	6.1	12.0	5.4	6.6
M. W.	24	I	12.8	7.5	5.3	11.0	6.5	4.5	9.8	4.8	5.0
B. M.	24	I	10.3	6.0	4.3	10.0	5.2	4.8	9.2	4.0	5.2
G. H.	25	II	12.6	6.0	6.0	10.7	4.9	5.8	9.2	4.0	5.2
M. S.	25	II				11.4	4.9	6.5	9.6	4.4	5.2
S. M.	25	II	12.0	6.8	5.2	10.3	5.0	5.3	9.5	4.7	4.8
F. P.	25	III				13.5	6.5	7.0	10.7	5.6	5.1
L. T.	26	I				9.7	3.8	5.9	9.0	4.0	5.0
J. W.	26	II	12.5	7.0	5.5	11.3	6.6	4.7	10.8	5.5	5.3
R. L.	27	I	(10.0)	(5.0)	(5.0)	9.6	5.0	4.6	8.8	4.0	4.8
M. F.	27	I				10.5	4.3	6.2	9.7	4.0	5.7
L. W.	27	II	(14.0)	(10.0)	(4.0)	9.5	5.5	4.0	8.6	4.4	4.2
N. B.	28	II				14.6	7.4	7.2	12.3	6.0	6.3
M. E. S.	28	IV	(14.0)	(7.0)	(7.0)	13.3	7.1	6.2	10.0	4.8	5.2
M. W.	28	II	12.4	8.0	4.4	11.2	6.8	4.4	8.8	4.3	4.5
R. P.	28	II	(13.0)	(8.0)	(5.0)	12.8	6.8	6.0	11.5	6.0	5.5
L. M.	28	III	(13.0)	(8.0)	(5.0)	12.3	6.7	5.6	11.4	6.4	5.0
F. R.	29	III	11.5	5.5	5.0	11.2	5.8	5.4	10.5	4.8	5.7
C. J.	30	III	(10.0)	(8.0)	(2.0)	10.9	6.0	4.9	11.5	5.7	5.8
L. E.	31	I	13.0	6.3	6.7	11.0	5.7	5.3	10.0	4.7	5.3
E. E.	32	V	12.0	8.0	4.0	10.5	6.0	4.5	9.4	4.2	5.2
L. C.	32	III	10.3	6.0	4.3	9.2	4.5	4.7	8.0	3.8	4.2
E. M.	35	II	10.5	5.0	5.5	9.3	4.5	4.8	9.2	4.2	5.0

*The average time per patient per trimester, rather than individual readings, are here presented. Each average used represented at least two, and mostly five to eight, separate measurements during the trimester. The values enclosed in parentheses represent single determinations and were not used in determining the final averages.

onds. In the final trimester the arm-to-tongue values fell between 8 and 16.2 seconds, averaging 10.2 seconds, and the arm-to-lung time range was 3.8 to 6.6 seconds, averaging 5 seconds. Table II indicates the ranges and averages of the circulation times in the three trimesters.

In the first trimester (Table III) 90 per cent of the values for arm-to-tongue circulation time fell in the range of 10 to 14 seconds, 10 per cent ranging between 14 and 16 seconds, with no values below 10 seconds. In the second

TABLE II. RANGE AND AVERAGES OF THE CIRCULATION TIMES IN THE THREE TRIMESTERS OF PREGNANCY

STUDY	FIRST TRIMESTER			SECOND TRIMESTER			THIRD TRIMESTER		
	RANGE	AVER- AGE	*	RANGE	AVER- AGE	*	RANGE	AVER- AGE	*
Arm-to-tongue time	10.3 to 15.0	12.4	± 1.0	9.2 to 15.4	11.3	± 1.3	8.0 to 16.2	± 10.2	± 1.1
Arm-to-lung time	3.8 to 8.3	6.6	± 0.8	3.8 to 7.7	5.8	± 0.9	3.8 to 6.6	± 5.0	± 0.7
Lung-to-tongue time	4.0 to 8.0	5.8	± 0.9	4.0 to 8.4	5.5	± 0.7	4.0 to 10.3	± 5.3	± 0.5

*Standard deviations about the means.

TABLE III. DISTRIBUTION OF ARM-TO-TONGUE TIME VALUES IN THE THREE TRIMESTERS

ARM-TO-TONGUE TIME, SECONDS	FIRST TRIMESTER		SECOND TRIMESTER		THIRD TRIMESTER	
	NUMBER OF CASES	PER CENT	NUMBER OF CASES	PER CENT	NUMBER OF CASES	PER CENT
14.0 to 16.0	3	10	2	4	1	2
10.0 to 13.9	27	40	37	77	23	48
8.0 to 9.9	0	0	9	19	24	50
Total	30	100	48	100	48	100

trimester, only two average values (4 per cent) fell above 14 seconds, and 19 per cent of the average values were less than 10 seconds. In the third trimester, only one arm-to-tongue measurement exceeded 14 seconds, and 50 per cent of the average values were shorter than 10 seconds.

In 45 of the 48 patients, there was a downward progression of the arm-to-tongue circulation time with each trimester. In only two cases did the average value obtained in the third trimester fail to be shorter than that obtained in the first trimester.

DISCUSSION

Repeated measurements of the velocity of blood flow in 48 pregnant women, who were followed from early in pregnancy to the conclusion of gestation, yielded values which fall within the accepted range for normal nonpregnant adults. The mean velocity of blood flow for the individual patient, as well as for the entire group, showed a progressive increase with each trimester, as recorded in Tables I and II. While the over-all range remained the same throughout pregnancy, the concentration of values for almost the entire group descended significantly within the range (Table III). These findings are in agreement with those of Cohen and Thomson,⁵ whose conclusions are based on a large series of cases.

The clinical value of the measurement of blood flow is dependent on the cooperation of the patient, and on the technique (such as rapidity of injection, size of needle employed, and type of solution). In addition, repeated observations assume a clinical significance that cannot be compared with single observations.

The discrepancies that exist in our results as compared with those in the literature may be more apparent than real. The conclusions made by Klee² based on the use of the fluorescein method may be due to the method alone. By this method, the determination of the velocity is dependent on the com-

pletion of the circulation after the dye traverses the capillary bed. It is well known that in pregnancy the circulation time through the capillary bed is significantly prolonged.⁴ When corrected for this factor, Klee's results agree with those noted by Cohen and Thomson, and with our own observations.

The differences noted by Spitzer,¹ Landt and Benjamin,⁷ and Greenstein and Clahr,⁸ may be due to the fact that only single observations were made on small groups of patients. Circulation values in the first trimester were not available, and comparable measurements in the subsequent trimesters of gestation were not always recorded. Additional evidence that the velocity of blood flow is increased during pregnancy is supplied by Burwell and Strayhorn,⁹ and Burwell and his co-workers,¹⁰ who demonstrated the decreased arteriovenous oxygen difference compared with the increased cardiac output. The role of the placenta as a modified arteriovenous fistula has been discussed.¹¹

The results of the present study indicate that values accepted for non-pregnant adults are the same as the range noted throughout pregnancy. The mean value for the group, however, showed a definite increase in velocity. This fact may be of clinical significance, for, as shown by Hamilton and Thomson,¹² the greatest incidence of heart failure occurs in the latter part of the second and the early part of the third trimester. Heart failure tends to decrease the velocity and hence to prolong the circulation time. As shown by this study, the pregnant state modifies this tendency in the direction of increasing the velocity of blood flow. When obtained in the second and third trimesters, circulation values in the upper limits of normal may no longer indicate an efficient circulation in the pregnant cardiac patient.

SUMMARY AND CONCLUSIONS

Forty-eight pregnant women were followed throughout the three trimesters of gestation. The velocity of blood flow, measuring arm-to-tongue, arm-to-lung, and lung-to-tongue times, was recorded during that period. Throughout pregnancy, the velocity of blood flow corresponded with the established normal values for nonpregnant adults. Beginning with the second trimester, the velocity of blood flow increased, and the mean values were the shortest in the third trimester of pregnancy.

The present data indicate that pregnancy modifies the velocity of blood flow and tends to decrease the circulation times. Circulation time values, therefore, at the upper limits of the usually accepted normal, may in pregnancy be an early manifestation of cardiac decompensation. Such results are of increased significance when similar values are obtained on repeated measurements.

REFERENCES

1. Blumgart, H. L., and Weiss, S.: Clinical Studies on Velocity of Blood Flow. IX. The Pulmonary Circulation Time, the Velocity of Venous Blood Flow to Heart, and Related Aspects of Circulation in Patients With Cardiovascular Disease, *J. Clin. Investigation* 5: 343, 1928.
2. Klee, F.: Die Strömungsgeschwindigkeit des Blutes in der Schwangerschaft, *Ztschr. f. Geburtsh. u. Gynäk.* 88: 308, 1924.
3. Koch, E.: Die Strömungsgeschwindigkeit des Blutes, *Deutsches Arch. f. klin. Med.* 140: 39, 1922.

4. Spitzer, W.: Die Blutströmungsgeschwindigkeit in normaler und gestörter Schwangerschaft. Beitrag zur Funktionsprüfung des Herzens in der Schwangerschaft und vor der geburt, Arch. f. Gynäk. 154: 449, 1933.
5. Cohen, M. E., and Thomson, K. J.: Studies on the Circulation in Pregnancy. I. The Velocity of Blood Flow and Related Aspects of the Circulation in Normal Pregnant Women, J. Clin. Investigation 15: 607, 1936.
6. Robb, G. P., and Weiss, S.: A Method for the Measurement of the Velocity of the Pulmonary and Peripheral Venous Blood Flow in Man, AM. HEART J. 8: 650, 1933.
7. Landt, H., and Benjamin, J. E.: Cardiodynamic and Electrocardiographic Changes in Normal Pregnancy, AM. HEART J. 12: 592, 1936.
8. Greenstein, N. M., and Glahr, J.: Circulation Time Studies in Pregnant Women, Am. J. Obst. & Gynec. 33: 414, 1937.
9. Burwell, C. S., and Strayhorn, W. D.: Observations on the Circulation During and After Pregnancy, J. Clin. Investigation 12: 97, 1933.
10. Burwell, C. S., Strayhorn, W. D., Flickinger, D., Corlette, M. B., Bowerman, E. P., and Kennedy, J. A.: Circulation During Pregnancy, Arch. Int. Med. 62: 97, 1938.
11. Burwell, C. S.: The Placenta as a Modified Arteriovenous Fistula, Considered in Relation to the Circulatory Adjustments to Pregnancy, Am. J. M. Sc. 195: 1, 1938.
12. Hamilton, B. E., and Thomson, K. J.: The Heart in Pregnancy and the Childbearing Age, Boston, 1941, Little, Brown & Company.

ACUTE PERICARDITIS IN YOUNG ADULTS

CAPTAIN RICHARD M. NAY, M.C., AND CAPTAIN NORMAN H. BOYER, M.C.

THE following report concerns the clinical courses of forty-six patients with pericarditis. A review of these cases was undertaken to obtain information concerning the early clinical differentiation between acute pericarditis due to rheumatic fever and pericarditis of so-called idiopathic etiology. In addition, the differential features of acute pericarditis and acute infarction of the myocardium are reviewed.

The patients were studied at one of the Army's Rheumatic Fever Centers. Forty-two patients had had their acute attack of pericarditis in other hospitals and had been transferred to this hospital at some time during their convalescence. Four patients were in this hospital at the time of the attack, or were admitted during the acute stage.

The patients were all men. Their ages ranged from 18 to 37 years and averaged 25 years. Thirty-eight patients were in the third decade of life and seven were in the fourth decade. The diagnosis of pericarditis was made on the basis of the clinical history, electrocardiograms, and roentgenograms of the chest. In 29 patients, pericardial effusion was demonstrable by x-ray examination. In 12 patients, no effusion was detected, but the presence of a friction rub and electrocardiographic patterns of the type associated with pericarditis gave adequate proof of the diagnosis. In five patients, x-ray films were not made during the acute phase of the illness, but the diagnosis was adequately established by other evidence. No patients were included in which there was the slightest doubt as to the presence of pericarditis.

It readily became apparent that the cases studied could be classified into three general groups. In the first group, which comprised the majority of the cases, pericarditis complicated an attack of acute rheumatic fever. Cases of acute pericarditis which were not associated with any specific etiological factor constituted the second group. The third group included cases of miscellaneous etiology.

Group 1.—Twenty-five cases of pericarditis due to rheumatic fever constitute Group 1. The average age of the patients was 25.6 years with extremes of 18 and 37 years. Six patients had a history of previous attacks of rheumatic fever, two had attacks which may have been rheumatic fever, and one had chorea. None of the patients were known to have had valvular heart disease prior to the present attack of rheumatic fever.

In 22 instances, pain in the joints preceded the symptoms of pericarditis. The time interval between the two varied from 1 day to 3 months, but in 17 cases the interval was 1 to 12 days. In the remaining five cases, the intervals

were 15, 17, 20, 30, and 99 days. The symptoms of pericarditis antedated the joint symptoms in only three instances. In these the time intervals were 5, 6, and 7 days.

In 18 instances, the onset of pericarditis was acute. It was frequently ushered in by a chill followed by fever and moderate to severe precordial or substernal pain. All of these patients noted increase in the pain on deep breathing, and many had pain on swallowing and on twisting the trunk. Pericardial friction rubs were heard in 14 patients at or soon after the onset of symptoms. Seven patients had no subjective symptoms of pericarditis except very mild precordial pain. Two of these patients had a friction rub.

The onset of pericarditis was usually accompanied by a transient leucocytosis; in 20 cases, the white blood cell count numbered 10,000 to 29,000 cells per cubic millimeter. In two instances, the white blood cell counts were normal (5,800 and 7,450) when pericarditis was diagnosed, and, in the remaining three cases, counts were not made at the onset of symptoms of pericarditis. In all instances, the leucocytosis was of short duration; it usually lasted less than one week.

The sedimentation rates were not altered appreciably by the onset of pericarditis. There was a secondary increase from 13 mm. to 32 mm. per hour (Wintrobe) in one case in which pericarditis occurred three months after the onset of rheumatic fever. This patient was considered to be in a virtually inactive stage of rheumatic fever at the time at which pericarditis occurred. In this case, the sedimentation rate remained elevated for fourteen days.

In 22 cases, x-ray films were taken during the acute stage of the pericarditis and in 13 instances pericardial effusion was demonstrated. Electrocardiograms were taken in all cases. In 17 instances, the patterns were considered to be diagnostic of pericarditis, and in 8 instances they were suggestive of pericarditis. The specific electrocardiographic changes will be discussed later since they were similar in all groups.

Six of the patients who had pericarditis associated with rheumatic fever have subsequently developed valvular heart lesions. Four patients have mitral insufficiency and a fifth has aortic insufficiency. The sixth patient has mitral stenosis and insufficiency and aortic insufficiency. This incidence (24 per cent) is no greater than that of the patients who developed valvular lesions among the entire group who had rheumatic fever at this hospital.¹ Data from these cases are summarized in Table I.

Group 2.—Fifteen cases of acute pericarditis in which the etiology was undetermined constitute Group 2. The patients in this group had none of the stigmata of rheumatic fever either before, during, or after the acute episode of pericarditis. We have designated this type as *pericarditis of undetermined etiology*.

The average age of the patients in this group was 27 years with extremes of 20 and 37 years. None of the patients had any history of previous attacks of rheumatic fever or chorea. None were known to have had valvular heart disease prior to their illness, and none had any evidence of valvular lesions

TABLE I. GROUP 1. FINDINGS IN TWENTY-FIVE PATIENTS WITH PERICARDITIS ASSOCIATED WITH ACUTE RHEUMATIC FEVER

CASE	AGE (YRS.)	PREVIOUS RHEUMATIC FEVER	DAY OF ONSET PERICARDITIS	HIGHEST WBC	HIGHEST ESR	FRICTION RUB	PERICARDIAL EFFUSION	ST	ELECTROCARDIOGRAM A-V TALE	RESIDUAL VALVE LESION
1	22	No	99	10,500	38	Present	Absent	Suggestive	First degree block	None
2	22	No	7	17,650	117	Present	Present	Suggestive	Normal	None
3	23	No	-6	10,600	28	Present	Present	Diagnostic	Normal	None
4	27	No	-3	17,000	30	Absent	Absent*	Diagnostic	Normal	None
5	27	No	-7	13,000	116	Absent	Present*	Diagnostic	Normal	None
6	25	No	8	13,700	25	Absent	Present*	Diagnostic	Normal	Mitral insufficiency
7	35	Questionable	6	16,900	57	Present	Present*	Suggestive	Normal	Mitral insufficiency
8	27	Chorea	3	20,300	56	Present	No x-ray	Suggestive	Normal	Mitral stenosis and insufficiency; aortic insufficiency
9	24	No	15	10,000	38	Present	Absent*	Suggestive	First degree block	None
10	27	No	12	21,900	57	Present	Present	Suggestive	Normal	None
11	23	Three separate attacks	8	13,000	52	Present	Present	Diagnostic	Normal	None
12	24	No	7	13,950	34	Absent	Present	Diagnostic	Normal	None
13	25	No	1	7,450	52	Present	Present	Diagnostic	Normal	None
14	24	Two separate attacks	10	12,100	36	Absent	No x-ray	Suggestive	Normal	None
15	22	No	20	12,250	67	Present	Present	Diagnostic	First degree block	None
16	18	Probable	5	15,800	33	Present	Present	Diagnostic	Second degree block	None
17	25	Questionable	2	Not recorded	Not recorded	Absent	Present*	Diagnostic	Normal	None
18	20	No	8	Not recorded	Not recorded	Present	Present*	Diagnostic	Normal	Mitral insufficiency
19	25	No	10	16,600	35	Absent	Absent*	Diagnostic	Normal	Aortic insufficiency
20	31	No	3	15,000	52	Present	Present*	Diagnostic	First degree block	None
21	19	Two separate attacks	9	5,800	56	Present	Present*	Diagnostic	Second degree block	Mitral insufficiency
22	37	No	12	11,050	32	Absent	Present*	Diagnostic	Second degree block	None
23	24	No	7	17,950	61	Present	No x-ray	Suggestive	First degree block	None
24	32	One attack	6	11,150	40	Absent	Absent	Diagnostic	Normal	None
25	27	Three separate attacks	6	29,600	58	Present	Present	Diagnostic	Second degree block	None

*Roentgenograms in these cases were not available for review, but the reports are quoted.

when examined. In 12 instances, the onset of pericarditis was extremely abrupt with sudden severe precordial or substernal pain and usually with chills and fever. The pain was aggravated by deep respiration and by twisting the trunk or swallowing. The pain was worse in the prone position, and the patients were more comfortable in a sitting position. Codeine and morphine were used frequently because of the severity of the pain. The acute symptoms usually subsided within forty-eight hours. In three cases, the onset extended over a period of three or four days during which the patient noted gradually increasing dyspnea and precordial pain.

Transient or persistent pericardial friction rubs occurred in 11 of the 15 patients. Leucocytosis was exceptional, and only four of the patients had a white blood cell count above 9,000 per cubic millimeter at any time during their illness. The highest counts in these four cases were 12,000, 21,000, 16,000 and 33,000, respectively. In the latter case, the patient was quite ill and had nausea, vomiting, and acute nasopharyngitis. Sedimentation rates were determined frequently in only nine cases. They were normal in three patients, and in six patients the highest rates varied from 29 to 78. Increase in the rate of sedimentation lasted from one to six weeks.

X-ray films of the chest were taken in 13 cases, in ten of which pericardial effusion was apparent. Frequent electrocardiograms were taken in 14 cases and were available for review. In each instance, the pattern was considered to be unmistakably that of pericarditis. The fifteenth patient was in a small dispensary during the acute phase of his illness and an electrocardiograph was not available until four weeks after the onset of his illness. At that time, the electrocardiogram was normal. Details of the electrocardiographic patterns are discussed below. Data from these cases are summarized in Table II.

TABLE II. GROUP 2. FINDINGS IN FIFTEEN PATIENTS WITH PERICARDITIS OF UNDETERMINED ETIOLOGY

CASE	AGE (YRS.)	FRICTION RUB	HIGHEST WBC	HIGHEST ESR	PERICARDIAL EFFUSION	ELECTROCARDIOGRAM	
						STT	A-V TIME
26	21	Present	8,000	Not re- corded	Present	Diagnostic	Normal
27	20	Absent	6,750	7	Absent	Diagnostic	Normal
28	23	Present	6,100	7	Absent	Diagnostic	Normal
29	29	Present	9,000	42	Absent	Diagnostic	Normal
30	24	Present	16,000	78	Present	Diagnostic	Normal
31	24	Absent	7,500	29	Present	Diagnostic	Normal
32	21	Present	8,200	40	Present	Diagnostic	Normal
33	27	Present	12,300	51	Present	Diagnostic	Normal
34	24	Present	21,000	3	Present	Diagnostic	Normal
35	20	Present	33,650	38	Present	Diagnostic	Normal
36	22	Present	9,500	34	Present	Diagnostic	Normal
37	26	Present	Not re- corded	Not re- corded	Not taken	Not taken	
38	22	Absent	7,600	Not re- corded	Present*	Diagnostic	Normal
39	37	Present	Not re- corded	Not re- corded	Not re- corded	Diagnostic	Normal
40	33	Absent	Not re- corded	36	Present*	Diagnostic	Normal

*Roentgenograms in these cases were not available for review, but the reports are quoted.

Group 3.—This group includes miscellaneous types of pericarditis. One patient had recurrent pericarditis with effusion and pleuritis with effusion, one had pericardial effusion accompanying atypical pneumonia, one had chronic constrictive pericarditis, one had pericarditis associated with an aneurysm of the ascending aorta, one had pericarditis which followed trauma to the chest, and one had pericarditis associated with acute glomerulonephritis. These cases had no common features except the presence of pericarditis.

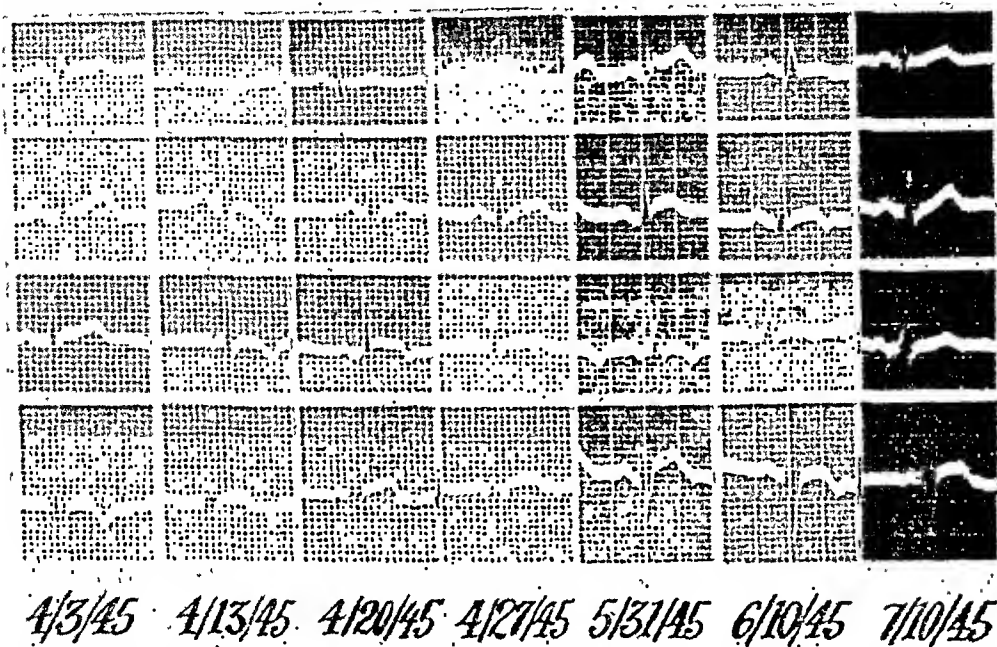


Fig. 1.—Case 41. Recurrent pericarditis with effusion and pleurisy with effusion. Illness began on March 24, 1945. The first electrocardiogram, taken April 3, 1945, shows elevation of the S-T segment in Leads I and II. Ten days later the T waves were inverted in all leads. The patient had recovered and the electrocardiogram was normal on April 27, 1945. The patient again became ill with pericardial and pleural effusions on May 28, 1945. The features of pericarditis reappeared in the electrocardiogram on June 10, 1945, and a normal tracing was obtained July 10, 1945. T-wave inversion occurring simultaneously in all four leads was present in eight cases in this series.

CASE 41.—This is the case of a soldier, aged 28 years, whose past history included an attack of pleurisy without effusion in 1935. In October, 1944, he had an attack of pericardial and pleural effusion. Spontaneous recovery occurred and he was returned to duty. On March 24, 1945, while overseas, he had sudden severe substernal pain and dyspnea. He was admitted to a hospital where a diagnosis of pericardial and bilateral pleural effusion was made. Electrocardiograms taken during this episode are reproduced in Fig. 1. Characteristic changes, including slight elevation of S-T segments in Leads I and II, followed by negative T waves in Leads I, II, and III were present. T₁ was diphasic in the tracing taken on April 13, 1945. The electrocardiogram had returned to normal by April 27, 1945. The patient was evacuated to the United States. On May 28, 1945, he again became ill with recurrence of the pericardial and pleural effusions. These effusions were apparent by roentgenography until June 28, 1945. Electrocardiograms taken May 31 and June 10, 1945, revealed changes similar to those of the earlier episode. An electrocardiogram taken July 10, 1945, was normal (Fig. 1). No definite diagnosis was made in this case. Culture of fluid removed from the pleural cavities was negative, and injection of the fluid into guinea pigs revealed no evidence of tuberculosis.

CASE 42.—This 26-year-old soldier developed pericardial effusion demonstrated by roentgenography during the course of atypical pneumonia. A single electrocardiogram, taken during the first week of the effusion, was normal. Unfortunately, subsequent tracings were not obtained.

CASE 43.—This patient had chronic constrictive pericarditis of undetermined etiology. The electrocardiogram showed low voltage, and T waves were inverted in all leads. The liver was enlarged and venous pressure was increased (20 cm. of water).

CASE 44.—This 26-year-old Negro soldier gave a history of a positive serologic test for syphilis at the age of 18 years. The date of initial infection was not known. He was admitted to the hospital acutely ill and complaining of substernal pain and dyspnea. A friction rub was heard over the preeordium. Roentgenograms and fluoroscopic examination of the chest revealed pericardial effusion and an aneurysm of the ascending aorta. Electrocardiograms revealed serial changes typical of pericarditis. A pericardial paracentesis was done and 50 c.c. of grossly bloody fluid was obtained. Microscopic examination of the fluid revealed no acid-fast or pyogenic organisms. Culture and guinea pig inoculation of the fluid were negative. Recovery was rapid.

CASE 45.—This 27-year-old soldier was unloading oil drums when he was crushed between a filled drum and a truck. He was treated in a dispensary but refused hospitalization. He apparently recovered but two weeks later was taken ill with acute pericarditis. The course of his illness was brief and recovery was complete. The role of trauma in this instance is unknown.

CASE 46.—This 34-year-old soldier was admitted to a hospital with acute glomerulonephritis. Three days later there were signs of congestive heart failure. A roentgenogram revealed the presence of pericardial effusion. Electrocardiograms were characteristic of pericarditis.

Data from these cases are summarized in Table III.

TABLE III. GROUP 3. FINDINGS IN SIX PATIENTS WITH MISCELLANEOUS TYPES OF PERICARDITIS

CASE	AGE (YRS.)	ASSOCIATED CONDITION	FRICTION RUB	HIGHEST WBC	HIGHEST ESR	PERICARDIAL EFFUSION	ELECTROCARDIOGRAM	
							STT	A-V TIME
41	28	Bilateral pleural effusion	Absent	12,650	42	Present	Diagnostic	Normal
42	26	Atypical pneumonia	Absent	11,000	36	Present	Normal*	Normal
43	22	Constrictive pericarditis	Absent	Not recorded	49	Absent	Diagnostic	Normal
44	26	Aneurysm of aorta	Present	8,200	82	Present	Diagnostic	Normal
45	27	Trauma to chest	Present	13,550	34	Present	Diagnostic	Normal
46	34	Acute glomerulonephritis	Absent	10,400	41	Present	Diagnostic	Normal

*Only one electrocardiogram obtained.

ELECTROCARDIOGRAMS

In 43 of the 45 cases of acute pericarditis, electrocardiograms were taken in sufficient number and at the proper time to reveal changes associated with pericarditis. In all of these cases, the changes observed in the electrocardiograms were diagnostic or suggestive of pericarditis. However, in some instances, only one or two electrocardiograms were taken since the changes noted were sufficiently marked to corroborate the diagnosis. In 29 cases, electro-

cardiograms were taken at frequent intervals until the abnormalities had ceased to be present. These cases lend themselves to detailed review. In many instances electrocardiograms were made at two- and three-day intervals and in none was the interval longer than one week. A total of 248 electrocardiograms were studied. The leads taken in all cases included the standard limb leads and the apical lead, IVF. The following observations were made.

The earliest electrocardiographic abnormality noted was elevation of the S-T segments. This occurred in 12 of our cases and disappeared before the tenth day in all cases except one, in which it was present from the seventh to the

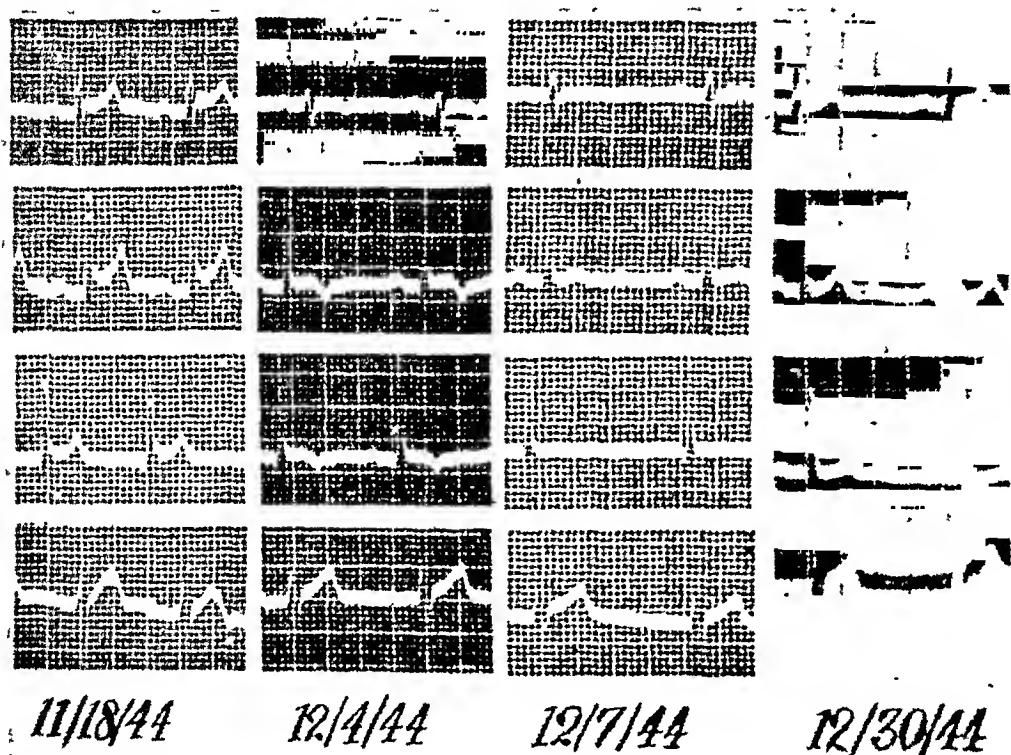


Fig. 2.—Case 34. The electrocardiogram of Nov. 18, 1944, was taken during the first twenty-four hours of the patient's illness. S-T segments in the standard leads are elevated, the ascending limb of the T wave is concave upward, and T is peaked. On Dec. 4, 1944, T₁, T₂, and T₃ were inverted and three days later, T₂ was upright and T₁ and T₃ were isoelectric. A normal electrocardiogram was obtained on Dec. 30, 1944. These electrocardiographic changes are typical of the patterns observed in this series of cases.

thirteenth day. In nine cases, electrocardiograms were not taken until after the tenth day following onset of symptoms, at which time it is improbable that S-T segment derangement would be encountered. Thus segmental elevation was noted in 12 (60 per cent) of 20 cases in which its occurrence could reasonably be expected. In six of the seven cases in which electrocardiograms were taken within twenty-four hours of the onset of symptoms, elevation of the S-T segments was noted. The elevation involved all four leads in two cases, Leads I, II, and IV in three cases; Leads I, II, and III in one case; Leads I and IV in one case; Leads II and III in one case; Leads I and II in two cases; Lead II in one case; and Lead I in one case. In no instance was there recipro-

cal depression of S-T segments of other leads. In four cases, associated with the elevation of the segments, there was a distinctive peaking of the T waves with upward concavity of the ascending limb of the wave. Attention has been directed to this feature by Barnes,² and it is well illustrated in Fig. 2.

When elevation of S-T segments occurred, it was transient, and a normal or near-normal tracing was usually obtained before changes in the T waves occurred. In a few instances the T waves were of very low voltage in the one or two electrocardiograms preceding that in which T-wave negativity occurred. Striking inversion of the T waves in multiple leads occurred in all except two of the cases studied. In eight cases, the T waves in all four leads were inverted simultaneously in at least one electrocardiogram. In 12 additional cases, T

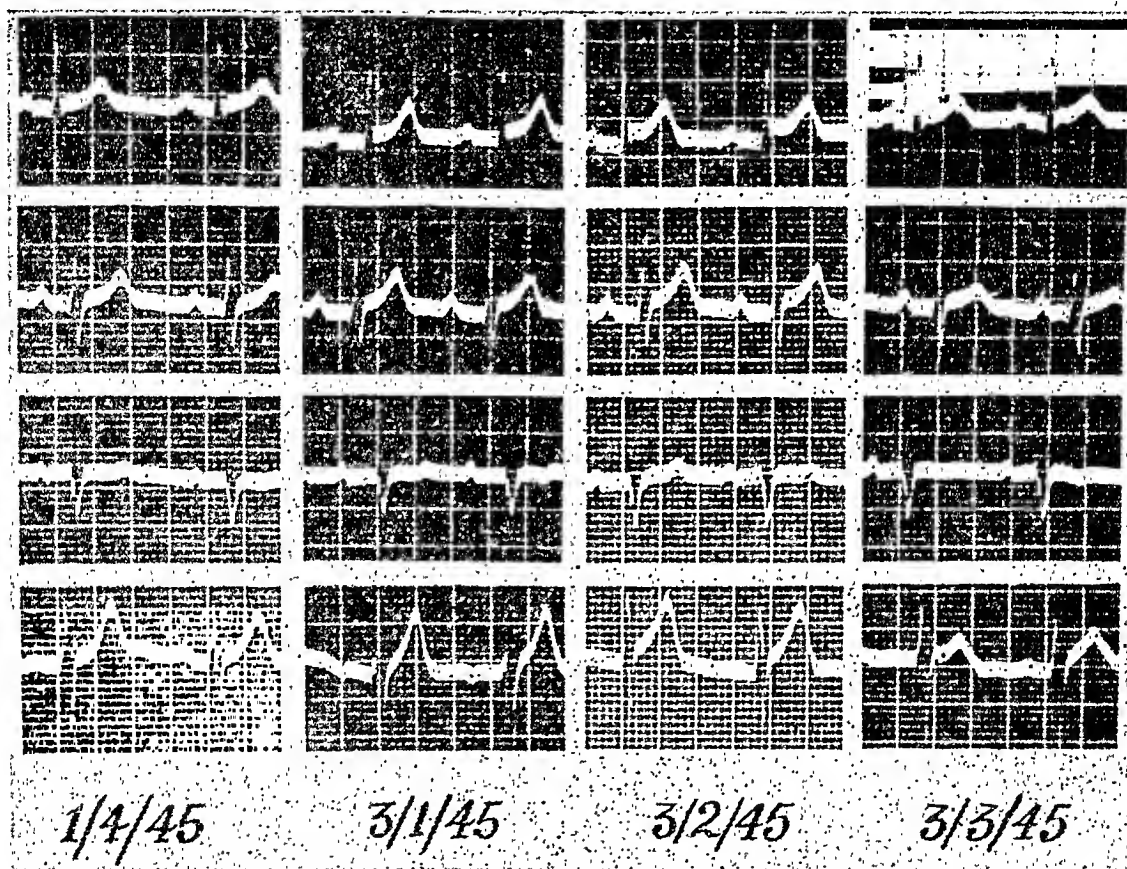


Fig. 3.—Case 1. The patient became ill with rheumatic fever in November, 1944. On March 1, 1945, he noted the sudden onset of substernal and precordial pain. A pericardial friction rub was present. An electrocardiogram, taken Jan. 4, 1945, was normal. Electrocardiogram taken March 1, 1945, revealed a slight elevation of S-T₁ and S-T₂ with peaked T waves in Leads I, II, and IVF. The P-R interval was 0.22 second. The following day the electrocardiogram was similar except that the P-R interval was 0.20 second. An electrocardiogram March 3, 1945, was normal. Although electrocardiograms were taken at weekly intervals for the five succeeding months, T-wave inversion did not occur. The changes illustrated are minimal. This type of electrocardiographic pattern, without T wave inversion, was present in two cases in this series.

waves in two or three leads were inverted, and the T waves in the remaining one or two leads were isoelectric or diphasic. Thus, in 20 (65 per cent) of the cases, the T waves were either negative, diphasic, or isoelectric in all four leads simultaneously. In seven other cases, T-wave inversion occurred in two or three leads without significant changes in the remaining leads, and in two cases, no abnormality of T waves was noted. Both of these cases had exhibited

distinctive elevation of S-T segments in the earliest tracings and clinically had unmistakable pericarditis of rheumatic etiology.

There was a marked variability in the onset and duration of abnormality in the T waves of the electrocardiograms in these cases. In 23 cases, inversion on the T waves was first noted between the fifth and eighteenth days. In the remaining four cases it occurred in the first, second, twenty-fourth, and twenty-seventh days. The duration of T-wave abnormality varied from its occurrence in a single tracing to occurrence over a period of seventeen weeks; in 21 cases T-wave negativity was present for two to nine weeks. In this connection it is interesting to note that the electrocardiograms of the patients in Groups 1 and 2 each demonstrated abnormalities for an average period of six weeks. However, it was observed that in the patients with rheumatic fever, T-wave changes generally occurred earlier in the course of pericarditis and persisted slightly longer than in patients without rheumatic fever.

Among the patients in Group 2 and Group 3, abnormality of auriculo-ventricular conduction was not observed. Among the 25 patients in Group 1, first degree heart block was present in five patients, and second degree block was present in four other patients. Thus, 36 per cent of patients who had pericarditis of rheumatic origin had conduction defects discernible by electrocardiographic methods. These conduction defects were transient in all but two cases. The first patient still had first degree block with the P-R interval varying from 0.24 to 0.28 second fifteen months after the onset of pericarditis. The sedimentation rate remained elevated and the patient had mild joint pains. In the second patient, second degree heart block was present during the acute stage of the illness and first degree block persisted for one year. The patient was discharged from the service despite the defect since he was well clinically and there had been no change in his condition for the preceding six months.

COMMENT

A comparison of the clinical course of patients in Groups 1 and 2 reveals that when pericarditis occurs during the course of rheumatic fever, it is less sudden in onset and the symptoms are less severe than in most cases of pericarditis of indeterminate etiology. In our patients, subjective and objective evidences of joint involvement were invariably associated with pericarditis of rheumatic origin. Indeed, this was the chief point of differentiation. In addition, joint manifestations usually antedated those of pericarditis, but in three instances, were delayed until a few days (one week or less) after the onset of pericarditis. Another interesting and valuable differential point is that rheumatic pericarditis usually is accompanied by a moderate leucocytosis (10,000 to 29,000) whereas no elevation of white blood cell count occurs in most cases of pericarditis of indeterminate etiology.

There was no appreciable difference in the occurrence or the amount of pericardial effusion in the two groups. Neither was there marked difference in the electrocardiographic findings, except that abnormalities in auriculoventricular conduction appeared in nine (36 per cent) of 25 patients who had rheu-

matic fever. It is worthy of note that in only 24 per cent of patients with rheumatic fever were there valvular lesions at the time of our last examination. This is in contrast to the findings of Massie and Levine,³ who examined 70 patients who had had rheumatic fever and pericarditis an average of seven years previously. Sixty-four per cent of these patients had valvular lesions at the later date. It is possible that valvular lesions will become apparent in our patients in future years. The duration of electrocardiographic abnormalities was approximately the same in the three groups of cases of acute pericarditis.

We have been impressed by the fact that the electrocardiographic patterns observed in these cases have been highly specific. There has been no confusion of these patterns with the patterns of myocardial infarction. We have not seen S-T segment elevation in the electrocardiograms of patients with rheumatic fever in the absence of pericarditis. Recently there has come under observation a 34-year-old soldier with acute rheumatic fever whose electrocardiograms revealed T-wave negativity in all leads. The pattern of serial electrocardiograms was similar to those seen in this series of cases. A friction rub was not noted during the early stage of the patient's illness. Roentgenograms of the chest were not taken, but clinically there was no evidence of pericardial effusion. With this possible exception, T-wave abnormalities suggestive of pericarditis were not found in any patients who had rheumatic fever without pericarditis in this hospital, although the number of patients in whom a diagnosis of rheumatic fever has been made now exceeds 900.

Among the group of 29 patients whose serial electrocardiograms were studied, there were eight patients in whom the electrocardiograms were normal after the onset of pericarditis. In 25 cases, T-wave abnormalities did not occur prior to the fifth day. In four cases, characteristic elevation of the S-T segments was noted in the earliest tracings. The importance of taking frequent electrocardiograms is emphasized by the fact that, in our series, normal electrocardiograms were obtained as long as two or even three weeks after the onset of pericarditis.

It is noteworthy that first degree block has persisted in two of our cases since Massie and Levine reported that, in rare instances, permanent conduction defects persist for years following rheumatic pericarditis. This occurrence has not been noted among other patients with rheumatic fever at this hospital.

In general, the electrocardiographic patterns have conformed to those described by other authors⁴⁻⁶ as occurring in acute pericarditis. Characteristic electrocardiograms have been obtained, however, in a larger proportion of cases, possibly because of the large number of tracings which were taken. The peculiar type of T-wave inversion noted by Bellet and McMillan⁵ occurred in three cases. This consists of a nearly normal ascending limb of the T wave to customary height, followed by a sharp, straight, descending limb which ends in a pointed inversion of T wave. This was encountered only in Leads I and II, and in each instance was associated with rheumatic fever.

Among the patients with pericarditis of indeterminate etiology, there were three who had been transferred to this hospital with diagnoses of myocardial

infarction. Eight others had been suspected of having rheumatic fever. The following points were found to be especially helpful in differentiation of acute pericarditis from acute myocardial infarction. In our patients, the age group was important since myocardial infarction is rare before the age of 35 years. The clinical course was also suggestive due to the fact that a friction rub is often heard in the first day in pericarditis, but is usually delayed for several days or a week in myocardial infarction. Important subjective symptoms in acute pericarditis were the aggravation of pain on breathing, swallowing, and twisting the trunk. These symptoms are rare in myocardial infarction and are almost pathognomonic of pericarditis.

In our experience, leucocytosis is uncommon in pericarditis of undetermined etiology but is usual in myocardial infarction. In patients with pericarditis, the height of the fever is compatible with an infectious process whereas the temperature is seldom more than slightly elevated in myocardial infarction, and the elevation rarely lasts longer than three days. Last, the electrocardiographic patterns produced by pericarditis may be distinguished from those of myocardial infarction. The chief electrocardiographic features of pericarditis are: elevation of S-T segments without reciprocal depression of other segments; late inversion of T waves in all of the standard leads and frequently in Lead IV as well; absence of prominent Q waves in the limb leads; absence of change in R wave in Lead IV; absence of frequent ventricular extrasystoles; and the return of the electrocardiogram to normal within eight or nine weeks in most cases.

SUMMARY

1. Forty-six cases of pericarditis occurring among young soldiers have been presented. In 25 cases, rheumatic fever was the etiological factor; in 15 cases, no definite etiology was determined; and in 6 cases, various etiological factors were present.

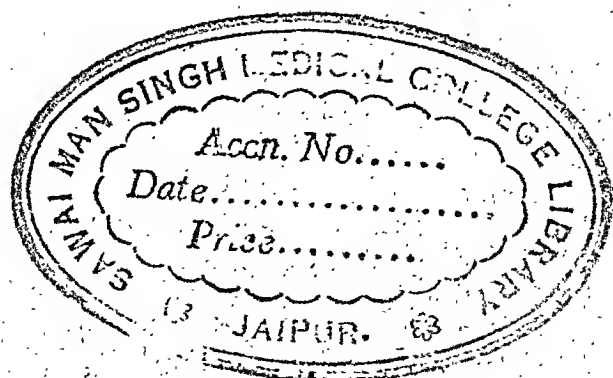
2. In this series of cases, the important points in the differentiation of acute pericarditis due to rheumatic fever from acute pericarditis of undetermined etiology were coincident joint manifestations and leucocytosis in the former, and the abrupt, severe onset and absence of leucocytosis in the latter.

3. The electrocardiographic patterns in 43 cases of acute pericarditis have been reviewed. Elevation of S-T segments occurred in 60 per cent of the cases in which electrocardiograms were taken within the first ten days after the onset of pericarditis. In all but two cases, T-wave changes of the distinctive pattern of pericarditis were present. The electrocardiograms returned to normal in four days to seventeen weeks. In eight (30 per cent) of 29 cases in which serial electrocardiograms were studied, normal tracings were obtained after the onset of pericarditis and prior to the appearance of changes in the T waves. This indicates the need for taking electrocardiograms over a period of three to six weeks following the onset of clinical symptoms. No difficulty was encountered in differentiating the electrocardiographic patterns of pericarditis from those of myocardial infarction or of rheumatic fever without pericarditis.

4. The differential diagnosis of acute nonrheumatic pericarditis and acute myocardial infarction has been discussed, and particular reference has been made to the difference in the electrocardiographic patterns produced by the two diseases.

REFERENCES

1. Boyer, N. H.: Electrocardiographic Abnormalities in Adults With Rheumatic Fever. To be published.
2. Barnes, A. R.: Electrocardiographic Patterns, Baltimore, 1940; Charles C Thomas.
3. Massie, E., and Levine, S. A.: The Prognosis and Subsequent Developments in Acute Rheumatic Pericarditis, J. A. M. A. 112: 1219-1223, 1939.
4. Noth, P. H., and Barnes, A. R.: Electrocardiographic Changes Associated With Pericarditis, Arch. Int. Med. 65: 291-320, 1940.
5. Bellet, S., and McMillan, T. M.: Electrocardiographic Patterns in Acute Pericarditis. Evolution, Causes, and Diagnostic Significance of Patterns in Limb and Chest Leads, A Study of 57 cases, Arch. Int. Med. 61: 381-400, 1938.
6. Vander Veer, J. B., and Norris, R. F.: The Electrocardiographic Changes in Acute Pericarditis. A Clinical and Pathological Study. AM. HEART J. 14: 31-50, 1937.



THE INCIDENCE OF RHEUMATIC FEVER AND HEART DISEASE IN SCHOOL CHILDREN IN DUBLIN, GEORGIA, WITH SOME EPIDEMIOLOGICAL AND SOCIOLOGICAL OBSERVATIONS

LIEUTENANT COMMANDER ROBERT W. QUINN, M.C., USNR

INTRODUCTION AND PURPOSE

CONSIDERABLE evidence supports the view that rheumatic fever is now the most important public health problem in the United States. We know that, in the United States, rheumatic fever accounts for more deaths than any other disease in the age group from 5 to 20 years, and moreover, deaths from rheumatic fever are on the increase.¹ Yet these mortality figures are only part of this problem. The decreased span of life and the economic loss resulting from the crippling of those who survive make the problem doubly challenging.

These facts have been brought into focus by our recent Selective Service figures and the rheumatic fever problem of the Armed Forces. In a re-examination of 4,994 men rejected for general military service because of cardiovascular defects, rheumatic heart disease was found to be by far the most common cause for rejection.² Large numbers of men have acquired rheumatic fever for the first time since entering the Armed Forces. In the Navy it has been necessary to establish hospitals exclusively for the care of patients with rheumatic fever. Although no exact figures are yet available, it is certain that many of these patients will develop rheumatic heart disease and thus add to the rheumatic fever problem. Meakins³ believes that rheumatic fever is the primary health problem in areas inhabited by the white man and states that tuberculous must take second place.

It is generally believed that the prevalence of rheumatic fever in the tropics and in the southern part of the United States is relatively low. Both Paul⁴ and Hedley,⁵ however, have pointed to the need for school surveys of heart disease, especially in the South. This study was undertaken to increase the knowledge of the prevalence of rheumatic fever.

DESCRIPTION OF DUBLIN AND ITS SCHOOL SYSTEM

Dublin, Georgia, the site of the U. S. Naval Hospital for Rheumatic Fever, seemed well suited for a survey of heart disease in school children since it is located in one of the southern states and the school population is composed of both white and Negro children living in the town or surrounding rural area. Dublin is located in Laurens County near the geographical center of Georgia, at a latitude of 42½ degrees and a longitude of 83 degrees. The elevation is 234 feet. The annual rainfall is approximately 50 inches; recent figures were 47.03 inches for 1943 and 50.84 inches for 1944. The temperature is relatively

high, with a mean temperature of 58.6° F. for the winter, 66.8° F. for the spring, 80.1° F. for the summer, and 66.4° F. for the fall. Laurens County covers an area of 796 square miles and had a population, in 1940 of 33,606. Among Georgia counties, Laurens County is seventh in size and seventh in population.⁶ In 1945 the population of Dublin was approximately 9,000. The population of both Laurens County and Dublin has fluctuated considerably in the past two years because of transient labor and Naval personnel associated with the building and operation of the U. S. Naval Hospital near Dublin.

The school system of Dublin is composed of three elementary schools and one high school for white children; and one elementary and one combination elementary and high school for Negro children. The total enrollment for the school year 1944-45 was as follows:

	Total Enrollment	Average Daily Attendance
White	1,132	902
Negro	722	596
Total	<u>1,854</u>	<u>1,498</u>

The enrollment of pupils in the fifth, sixth, seventh, and eighth grades was 299 boys and 347 girls, totaling 646. The average daily attendance in these respective grades in the schools for white children was 367 and in the combined elementary and high school for Negro children was 166.

Of the total number of registered school children in Dublin, 26.7 per cent were examined. However, with the constantly changing school population, perhaps the average daily attendance gives a more accurate figure of the number of children available; of this number approximately one-third were examined. Seventy-two per cent of the total number of children in the fifth, sixth, seventh, and eighth grades were examined. Children in these grades were selected because it was thought that from them an adequate sampling of the age group in which rheumatic heart disease is most likely to occur could be obtained. The children selected are beyond the average age of onset of rheumatic fever (7 to 9 years); moreover, they are old enough to exhibit some of the manifestations of rheumatic heart disease should they have acquired rheumatic fever at an earlier age. It is true that in an older group of children more of those susceptible to rheumatic fever would have acquired the disease than in a younger group. However, this number would probably not be large enough to change materially the over-all incidence of rheumatic fever or rheumatic heart disease.

TECHNIQUE

The data used in this study were obtained from school children of the fifth, sixth, seventh, and eighth grades of both the white and Negro schools. The form used in recording this data is shown in Fig. 1. After the consent of the parents was obtained, groups of 15 to 20 children stayed after school in the afternoon for examination. A complete history for rheumatic fever was obtained from the child or parent, followed by a brief general physical examination and a careful examination of the heart. Each child was examined un-

NAME	AGE	SEX	RACE: Color
			Extr.
ADDRESS	PARENT'S NAME		
P.H.	Born:		
	Rheumatic fever:	Age:	No of attacks: Place of origin:
	"Blue baby":		
	Chorea:		
	Joint swelling, pains, redness or tenderness:		
	"Growing pains":		
	Nose bleeds:		
	Fever:		
	Loss of weight, recent, or failure to gain:		
	Abdominal pain:		
	Nodules in skin:		
	Tonsillitis:		
	Strep. sore throat:		
	Scarlet fever:		
	Diphtheria:		
	Whooping cough:		
	Heart Disease:		
	Skin lesions:	Purpura:	Erythema
	Exercise tolerance:		
	Pulmonary disease:		
	Allergy:		
	Diet:		
F.H.	Rheumatic fever:	Cardiac disease:	Chorea:
	No. of siblings	Allergy:	
Social History:			
	Home: Where	Country or town:	
	Number of persons living there:		
	Number of rooms:		
	Dampness:		
	Financial status:		
	0 - 1,000		
	1,000 - 2,000		
	2,000 - 3,000		
	3,000 - Plus		
P.E.	Temperature:	Pulse:	Respiration: Blood Pressure:
	General description:		
	Lymphatic system:		
	Skin:		
	Respiratory system:		
	Cardiovascular system:	Cyanosis:	Clubbing: Idema: Cap. Pulse
	P.M.T: R.C.D:	A ₂ P ₂	1st Apical Sound:
Murmurs:	Intensity	Pitch	Quality
Base			Duration
L.S.B.			Time
Apex			Ex. Trans.
C.B.C.:			
Ecg:			
X-ray:			
Fluoroscopy:			
Impression:			
DATE		NAME	

Fig. 1.

dressed to the waist while standing, lying on his back, lying on the left side, and lying on the left side following exercise. When a definite diagnosis could not be made following a single examination, second and third examinations were made and electrocardiographic, fluoroscopic, and x-ray examinations were performed. When a history suggestive of past rheumatic fever was obtained, the child's parents were interviewed and the previous history was either corroborated or disqualified.

DESCRIPTION OF MATERIAL

Of the 401 school children examined, 237 (59.1 per cent) were white and 164 (40.9 per cent) were Negro. No exact figures concerning the racial extraction of the white children were obtained, but they were largely of Irish and English descent, their ancestors having settled here three or four generations ago. All of the children were born and grew up in Georgia or in the surrounding states (with the exception of one child born in New York City and two children born in southern California, none of whom had rheumatic fever). Of the white children, 113 (47.7 per cent) were male and 124 (52.3 per cent) were female. Of the Negro children, 41 (25.5 per cent) were male and 123 (74.5 per cent) were female (Table I). The average age of the white and of the Negro children was $12\frac{7}{12}$ years. It is noteworthy that the spread of ages in the Negro group was greater than in the white group.

TABLE I. NUMBER, RACE, AND SEX OF CHILDREN EXAMINED IN THE FIFTH, SIXTH, SEVENTH, AND EIGHTH GRADES

RACE	NUMBER	MALE	FEMALE
White	237	113	124
Negro	164	41	123
Total	401	154	247

FAMILY HISTORY

A history of rheumatic fever in the families of nine white children (3.7 per cent) was obtained, but none of the Negro children gave a family history of rheumatic fever. The question of family history of heart disease or heart trouble of any type resulted in an affirmative answer from 58 white children (24.4 per cent) and 20 Negro children (12.1 per cent).

SOCIAL HISTORY

Table II shows that the majority of the children lived within the city limits of Dublin, however, 31 (13 per cent) of the white children and 21 (12.8 per cent) of the Negro children were from rural districts. It was found that crowding existed in the homes of 74 white children (31.2 per cent) and 80 Negro children (48.7 per cent). Crowding arbitrarily was said to exist when

TABLE II. DESCRIPTION OF HOMES

RACE	TOWN	RURAL	CROWDING	DAMPNESS
White	206(87.0%)	31(13.0%)	74(31.2%)	11(4.6%)
Negro	143(87.2%)	21(12.8%)	80(48.7%)	16(9.7%)

the number of persons living in the house exceeded the number of rooms.* During and since the building of the U. S. Naval Hospital near Dublin, the population increase undoubtedly has added to the high incidence of crowding. Additional housing deficiencies which were present in many of these homes included absence of sunlight, dilapidation, fire hazards, inadequate washing and plumbing facilities, and poor heating.

Dampness was considered to exist when the home was located near a swamp or stream, or on low-lying ground where drainage following rains was poor and water stood under or around the house for days at a time. Eleven (4.6 per cent) of the homes of the white children and 16 (9.7 per cent) of those of the Negro children were classified as damp (Table II). The high annual rainfall makes dampness common in this area.

The economic status of the families of the children is tabulated in Table III. Estimates of the annual family income were determined from the occupation or profession of the family provider, the number of working days per year, and the number in the family contributing to the family income. However, the figures lent themselves readily to classification in the four income groups shown in Table III. They indicate that low incomes are common in Dublin, particularly among the Negroes.

TABLE III. ECONOMIC STATUS

INCOME GROUP	WHITE	NEGRO
Under \$1,000 per year	40 (16.9%)	101 (61.6%)
\$1,000-\$2,000 per year	98 (41.3%)	51 (31.1%)
\$2,000-\$3,000 per year	74 (31.2%)	11 (6.7%)
Over \$3,000 per year	25 (10.6%)	1 (0.6%)

RESULTS OF EXAMINATION

The results of the examination of 401 school children for evidence of heart disease are tabulated in Tables IV and V.

From Table IV it can be seen that 401 children represent approximately 33 per cent of the available school population. One hundred seventy-six of these children were classified as heart disease suspects. In this category are those with extrasystoles, functional murmurs, potential heart disease, and possible heart disease. They represent 43.8 per cent of all subjects, a rate which is consistent with the surveys of Sampson and his co-workers⁸ Christie,⁹ and Samp-

TABLE IV. INCIDENCE OF CONGENITAL AND RHEUMATIC HEART DISEASE IN 176 CARDIAC SUSPECTS FOUND AMONG 401 SCHOOL CHILDREN

SCHOOL POPULATION EXAMINED		HEART DISEASE SUSPECTS		ORGANIC HEART DISEASE		RHEUMATIC		CONGENITAL		RATES PER 1,000 SCHOOL POPULATION		
TOTAL	%	TOTAL	%	TOTAL	%	TOTAL	%	TOTAL	%	ORGANIC	RHEUMATIC	CONGENITAL
401	33	176	43.8	6	1.5	4	0.67	2	0.33	15	10	5

*The standard that indicates that dwellings are crowded when they are occupied by more than one person per room, is commonly used by housing officials and is regarded as a relatively high standard of measurement. It was used by the Division of Public Health Methods, National Institute of Health, U. S. Public Health Service, in its National Health Survey in 1935-36.

son, Christie, and Geiger,¹⁰ and with the consensus of pediatric experience in dealing with children.¹¹ Cardiac murmurs were found in a large number, 114 (48.1 per cent) of the white children and in 62 (37.8 per cent) of the Negro children. These were judged to be unexplained or "functional" murmurs and were all systolic in time. The most common location was along the left sternal border, the next most common was in the apical region, and the least common was at the base, in the pulmonary area. Combinations of basal, apical, or left sternal border murmurs were encountered occasionally. Unexplained murmurs were heard more frequently in girls, both white and Negro, than in boys.

Six children were found to have organic heart disease, an incidence of 1.5 per cent. Four of these had rheumatic and two congenital heart disease. Therefore, the incidence of rheumatic and congenital heart disease in the school population was 1 per cent and 0.5 per cent, respectively. It is interesting to note that 33 per cent of the subjects with organic heart disease had congenital lesions. This is in contrast to other reports,^{12, 15} which gave figures of 10 to 20 per cent, but is consistent with the reports of Sampson et al.⁸ and Sampson, Christie, and Geiger¹⁰ on the west coast.

The children with congenital or rheumatic heart disease and the cardiac disease suspects were classified further according to the anatomical and etiological criteria of the Criteria Committee of the New York Heart Association.¹⁶ The anatomical diagnoses were as follows: coarctation of the aorta, one case; aortic stenosis (congenital), one case; mitral insufficiency, three cases; and mitral stenosis and insufficiency, one case. Four children, two Negro and two white, who gave clear histories of rheumatic fever but had no physical findings of heart disease, were classified as having potential heart disease. Two white children and one colored child who had physical findings suggestive but not characteristic of heart disease and whose histories did not reveal any definite etiological factor were classified as having possible heart disease.

The rheumatic fever rate was arrived at by including the four subjects classified as having potential heart disease, from whom histories of rheumatic fever were obtained, the three cases of mitral insufficiency, and the one case of mitral stenosis and insufficiency.

The incidence of rheumatic fever and heart disease for both white and Negro children is shown in Table V. The incidence rate of rheumatic fever for all children studied was two per cent, for whites 2.1 per cent, and for Negroes 1.82 per cent. The incidence rate of rheumatic heart disease for the school population, determined from three cases with mitral insufficiency and one case with mitral insufficiency and mitral stenosis was 1 per cent. The rate of rheumatic heart disease in the white children is 1.26 per cent and in the Negro children 0.60 per cent.

TABLE V. PREVALENCE OF RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE IN 401 DUBLIN, GEORGIA, SCHOOL CHILDREN

	WHITE	NEGRO	TOTAL
Rheumatic Fever	5 (2.1%)	3 (1.82%)	8 (2.0%)
Rheumatic Heart Disease	3 (1.26%)	1 (0.60%)	4 (1.0%)

DISCUSSION

Factors of possible epidemiological importance in the five white children in the rheumatic fever group were as follows: Crowding was present in one home. Two children belonged to families with incomes below \$1,000 yearly, and the other three were in the \$1,000-\$2,000 income group. There was no family history of rheumatic fever among these children, dampness was not present in their homes, and their diets were considered to be fairly adequate. All three Negro children belonged to families with incomes less than \$1,000 yearly, crowding was present in one home, dampness was not present in any home, there was no family history of rheumatic fever, and the diets of all three were considered to be inadequate in certain respects.

The incidence of rheumatic heart disease (1 per cent) in Dublin, Georgia, is moderately high. Although the rheumatic heart disease rate in this community is not so high as in New England (2.2 per cent) or in Great Britain, it is higher than that found among the Indians of southern New Mexico (0.5 per cent)¹⁷ and among school children in parts of northern California, including San Francisco (0.22 per cent) and Redlands (0.32 per cent).⁸ In a recent study of the school children in three climatically different communities of northern California, by Sampson et al.,⁸ definite relations were found to exist between humidity, precipitation, and temperature and the incidence of heart disease. Dublin has a rather high humidity and a high precipitation, but a warm climate; and, as might be expected, the incidence of rheumatic heart disease here lies between the extremes of that of Redlands (0.32 per cent), with a warm dry climate, and that of Eureka (2.04 per cent,) with a cool climate and a high precipitation. It compares closely with the incidence found in Susanville (1.09 per cent), a mountainous community with average humidity and precipitation but with wide extremes of average winter and summer temperature. Chavez¹⁸ found that, in Mexico, with its diversified but predominantly subtropical climate, rheumatic heart disease is as prevalent as it is in England and the northern part of the United States. In view of this observation it is not surprising to find a rather high incidence of rheumatic fever and rheumatic heart disease in Dublin with its humid, warm climate. Such important factors in the epidemiology of rheumatic fever as low income, crowding, poor nutrition, and dampness all exist in Dublin and would lead one to expect that the incidence of rheumatic fever would not be low. Christie⁹ has pointed out that there is an unusually high hospital incidence of rheumatic fever in northern California, but a low general incidence. It would appear that the hospital incidence in Dublin is very low and the general incidence moderately high. None of the children with rheumatic heart disease or inactive rheumatic fever had ever been hospitalized for these illnesses, but three had consulted physicians. This suggests that the clinical manifestations of rheumatic fever in Dublin are rather benign, and agrees with the observation of Seegal, Seegal, and Jost,¹⁹ who determined that the yearly hospital admission rate for rheumatic fever in 24 United States hospitals decreased from latitude region 50 to 45 degrees to latitude region 34 to 29 degrees. However, the majority of the children in

Dublin were unable to afford hospitalization even if they had needed it. Mills²⁰ states that the disease strikes most frequently in more stormy portions of the temperate zones and is a more violent form of the infection there.

Rheumatic heart disease is the least common of the four major types of heart disease (hypertensive, arteriosclerotic, syphilitic, and rheumatic) which occur in the southern part of the United States. This fact is evident from both clinical and pathologic studies.^{21, 24} As in other parts of southern United States, in Dublin the incidence of rheumatic fever and rheumatic heart disease is lower in Negroes than in white persons. No figures are available concerning the death rate for rheumatic heart disease in Dublin, but according to Hedley⁵ the death rates from heart disease were lower, especially for white persons from 5 to 24 years of age, in the Deep South than for both races in the middle Atlantic and New England regions.

The number of children included in this study is too small to permit wide conclusions to be drawn, but probably a general idea of the status of rheumatic fever in Dublin can be gathered from these figures. Larger and more comprehensive studies are needed to obtain more extensive information on the incidence of rheumatic fever and rheumatic heart disease in the Southern States.

CONCLUSIONS

1. A cardiac survey of 401 school children in the fifth, sixth, seventh, and eighth grades in Dublin, Georgia, was made.
2. Six cases of organic heart disease were found, giving an incidence of 1.5 per cent. Of these, four had rheumatic heart disease and two had congenital heart disease.
3. The incidence of rheumatic heart disease was found to be 1 per cent for all children examined, 1.26 per cent for white children and 0.60 per cent for Negro children.
4. The incidence of congenital heart disease was 0.5 per cent.
5. The incidence of rheumatic fever was 2 per cent. The incidence in white children was 2.10 per cent and in Negro children 0.60 per cent.
6. Climatologic and socioeconomic factors such as dampness, crowding, inadequate housing, malnutrition, and low economic status, which are very important epidemiologically in rheumatic fever and rheumatic heart disease, were found to exist in Dublin, Georgia.
7. Similar but more extensive studies are needed to determine more accurately the incidence of rheumatic fever and rheumatic heart disease in different areas of the United States.

The cooperation of many persons is necessary in a survey of this type. I wish to thank Dr. Amos Christie for valuable constructive criticism and suggestions; Commander B. E. Goodrich, who aided in the examination of some of the doubtful cases; Mr. S. H. Sherman, superintendent of schools for Dublin, Hospital Corps Waves Iva M. Barber PhM3/c and Edith M. Townsend PhM2/c, who gave valuable help during the examination of the children, and my wife, who gave generously of her time.

REFERENCES

1. Armstrong, D. B., and Wheatley, G. M.: Studies in Rheumatic Fever, New York, Nov., 1944, Metropolitan Life Ins. Co.
2. Fenn, G. K., Kerr, W. J., Levy, R. L., Stroud, W. D., and White, P. D.: Re-Examination of 4,994 Men Rejected for General Military Service Because of the Diagnosis of Cardiovascular Defects, *AM. HEART J.* 27: 435, 1944.
3. Meakins, Jonathan C.: The Practice of Medicine, ed. 4, St. Louis, 1944, The C. V. Mosby Co.
4. Paul, J. R.: The Epidemiology of Rheumatic Fever, New York, 1943, Metropolitan Life Ins. Co.
5. Hedley, O. F.: Trends, Geographical and Racial Distribution of Mortality From Heart Disease Among Persons 5-24 Years of Age in the U. S. During Recent Years (1922-1936), *Pub. Health Rep.* 54: 2271, 1939.
6. Hart, B. S.: History of Laurens County, Georgia, 1807-1941, Athens, Ga., McGregor Co.
7. Personal communication from Sydney Maslen, Secretary, Committee on Housing, Community Service Society of New York.
8. Sampson, J. J., Hahman, P. T., Halverson, W. T., and Shearer, M. C.: Incidence of Heart Disease and Rheumatic Fever in School Children in Three Climatically Different California Communities, *AM. HEART J.* 29: 178, 1945.
9. Christie, Amos: Rheumatic Fever in Northern California, *AM. HEART J.* 12: 153, 1936.
10. Sampson, J. J., Christie, Amos, and Geiger, J. C.: Incidence and Type of Heart Disease in San Francisco School Children, *AM. HEART J.* 15: 661, 1935.
11. Holt and McIntosh: Diseases of Infancy and Childhood, ed. 11. New York, 1939, D. Appleton-Century Co.
12. Halsay, Robert H.: Heart Disease in Children of School Age, *J. A. M. A.* 77: 672, 1921.
13. Cahan, Jacob M.: The Incidence of Heart Disease in School Children, *J. A. M. A.* 92: 1576, 1929.
14. Robey, William H.: A Cardiac Survey of Children in Boston Public Schools, *Nation's Health* 9: 21, 1927.
15. Cohn, A. E.: Heart Disease From the Point of View of the Public Health, *AM. HEART J.* 2: 275, 1927.
16. Criteria Committee of the New York Heart Association: Nomenclature and Criteria for Diagnosis of Diseases of the Heart, ed. 4, New York, 1943. New York Heart Association.
17. Paul, J. R., and Dixon, C. L.: Climate and Rheumatic Heart Disease, *J. A. M. A.* 108: 2096, 1937.
18. Chavez, I.: The Incidence of Heart Disease in Mexico, *AM. HEART J.* 24: 88, 1942.
19. Seegal, David, Seegal, B. C., and Jost, E. L.: Comparative Study of Geographical Distribution of Rheumatic Fever, Scarlet Fever, and Acute Glomerulonephritis in North America, *Am. J. M. Sc.* 190: 383, 1935.
20. Mills, C. A.: Seasonal and Regional Factors in Acute Rheumatic Fever and Rheumatic Heart Disease, *J. Lab. & Clin. Med.* 24: 53, 1938.
21. Stone, C. T., and Vanzant, F. R.: Heart Disease as Seen in a Southern Clinic, *J. A. M. A.* 89: 1473, 1927.
22. Paullin, J. F.: Discussion of the above paper of Stone and Vanzant, *ibid.*
23. Holoubek, Alice B.: Heart Disease in the South. I. Statistical Study of 1,045 Cardiac Deaths, *AM. HEART J.* 29: 168, 1945.
24. Lawes, C. L.: Etiology of Heart Disease in Whites and Negroes in Tennessee, *AM. HEART J.* 8: 608, 1933.

Clinical Reports

ANOMALOUS ORIGIN OF THE LEFT CORONARY ARTERY FROM THE PULMONARY ARTERY; REPORT OF A CASE DIAGNOSED CLINICALLY AND CONFIRMED BY NECROPSY

S. EIDLOW, M.D., AND ELEANOR R. MACKENZIE, M.D.
MONTREAL, CANADA

THE first recorded case of a congenital circulatory defect in which the left coronary artery took anomalous origin from the pulmonary artery was described by Abrikosoff¹ in 1911. His observation concerned an infant, 5½ months old, who died of pneumonia and who disclosed at autopsy a large heart with myocardial fibrosis and aneurysmal dilatation of the left ventricle. Five years later, Heitzmann² reported an identical case and called attention to a striking similarity to the pathologic findings, observed in adults, which result from coronary sclerosis or occlusion.

Sanes and Kenny,³ in 1939, reporting a case of their own and reviewing five other cases with this anomaly, concluded that the clinical features presented are as typical as are the pathologic changes and deplored the fact that in none of the reported cases was an accurate diagnosis made during life. They suggested that establishment of this circulatory defect as a clinical entity would make ante-mortem diagnosis more likely. In their opinion the presence of this lesion should be suspected in patients presenting these characteristics.

A survey of subsequent literature lends some support to this view. A critical review of seventeen cases by Soloff,⁴ in 1942, led him to the conclusion that the majority of patients with this lesion present a sufficiently characteristic clinical picture to make ante-mortem diagnosis possible. On the other hand, the case reported by Proeseher and Baumann⁵ in 1944 did not present clinical features which readily suggested this anomaly. While the series of cases is still too small for the definition of criteria for accurate diagnosis, all these observations emphasize the importance of recognizing the occurrence of cardiac pain in infants and indicate electrocardiographic and radiologic studies as valuable aids in clinical diagnosis.

CASE REPORT

Clinical History (by S. E.).—The patient was a female infant born at the Royal Victoria Montreal Maternity Hospital on Feb. 17, 1945. Delivery was at term and was entirely normal. The family includes two other children, the younger of which, aged 5 years, suffers

From the Department of Pathology, Children's Memorial Hospital, and the Department of Pathology of McGill University.

Received for publication Oct. 15, 1945.

from bronchial asthma; the older child is normal. The father is alive and active. The mother, 33 years of age, has enjoyed good health except that for the past five years, she has suffered from amenorrhea, going as long as two years without a menstrual flow. She consulted me on Sept. 14, 1944, because of an abdominal mass. When told that the abdominal tumor was indeed a pregnancy, she expressed a fear that, because conception had occurred following a period of amenorrhea of about three months' duration, normal fetal development was unlikely. I assured her that this was not the case and that her fears were unfounded. However, immediately after delivery, I was called to see the newborn infant and thus had the opportunity of examining her at the age of only two days.

Examination at this time revealed an apparently normal infant. There was no cyanosis. The heart was not enlarged and no murmurs or abnormal sounds were heard; the rhythm was normal, and the rate was 150 per minute. The lungs were resonant throughout, and no râles or abnormal breath sounds were audible. I felt justified in reassuring the mother that there was no evidence of any anomaly. Dr. S. B. Shapiro then took charge of supervising the feeding and general care of the baby.

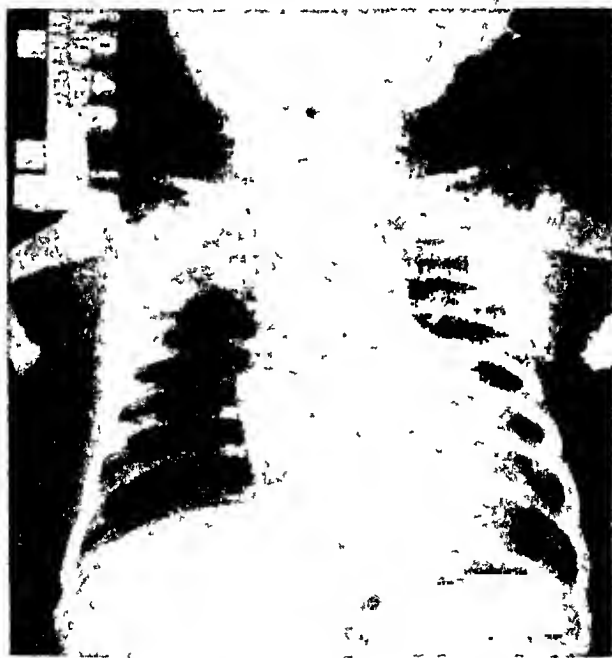


Fig. 1.—X-ray film shows heart enlarged to the left and also to the right. Its middle left border is very rounded. There is evidence of partial atelectasis of the upper lobe of the right lung.

I saw the infant for the second time on May 24, 1945, because of peculiar paroxysms observed by the nurse who had been caring for the infant since May 10. She had been told that the patient was a normal and healthy infant; however, she noticed that the baby rarely ate well and seemed uncomfortable while taking her feedings. After taking about an ounce of formula, she would seem to choke and to have difficulty in breathing and then would rest for several minutes before resuming her feeding. Small frequent feedings were therefore resorted to. There was a good deal of wheezing, but vomiting was not a feature; the infant was restless at night. During these two weeks, the nurse had observed five paroxysms of "shortness of breath, rapid pulse, flushed face which turned blue and then white, and profuse perspiration." These attacks lasted from four to eighteen minutes, and left the infant extremely weak. Dr. Shapiro was notified. He ordered an x-ray film of the chest, and, because of the history of bronchial asthma in the family, adopted treatment on the basis of a possible allergic manifestation.

Examination at this date revealed a 3-month-old infant, who apparently was normal in mental and physical development. The skin and mucous membranes were pale, but there was no cyanosis or clubbing of the fingers. The lungs were resonant throughout and no râles or abnormal breath sounds were heard. The heart, on percussion, revealed an increase in the area of cardiac dullness; the sounds, however, were normal and there were no murmurs; the rhythm was normal and the rate was 150 per minute. Posteroanterior and lateral x-ray films of the chest made at this time showed cardiac enlargement both to the left and to the right; the middle portion of the left border was unusually rounded. Partial atelectasis of the upper lobe of the right lung was also disclosed (Fig. 1).

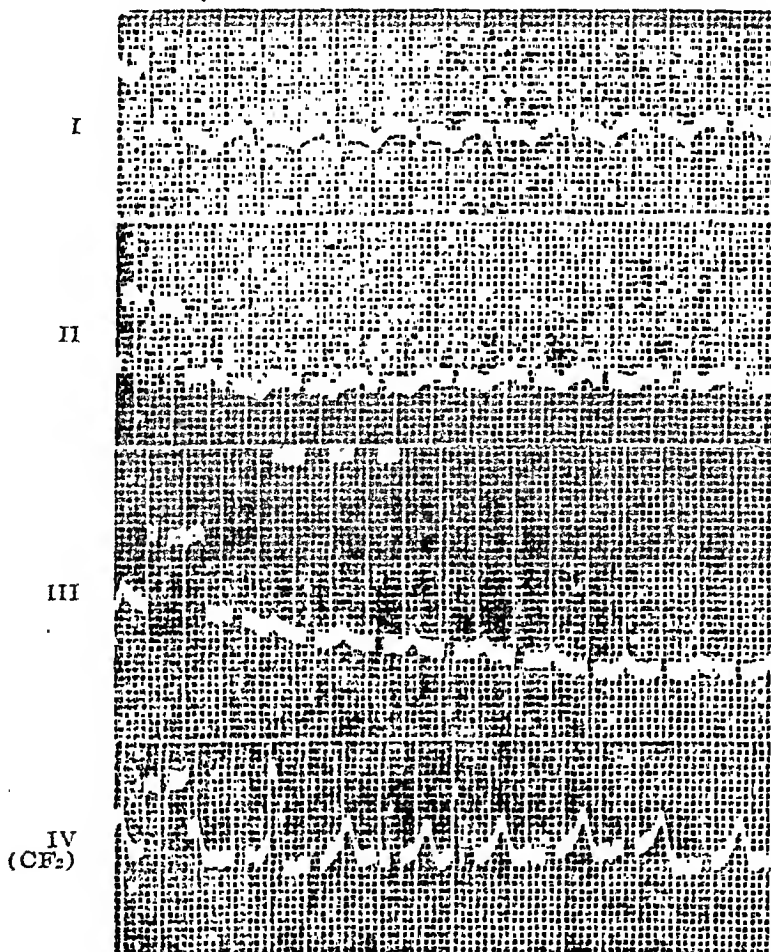


Fig. 2.—May 24, 1945. Normal rhythm. Rate, 150 to 167. P-R, 0.12 second. QRS, 0.06 second. Normal axis. S-T interval depressed in Leads I and II. Inverted T in Leads I and II; upright T in Lead IV. Diphasic QRS in Lead III.

The account given by the nurse of acute discomfort brought on by feeding, and of paroxysms of dyspnea, cyanosis, pallor, and sweating in the presence of a large heart, brought to mind the possibility of cardiac pain on the basis of an inadequate coronary blood supply, and I recalled reports in the literature of cases presenting a similar clinical picture. I took an electrocardiogram, which showed inversion of T waves in Leads I and II, no axis deviation, and an upright T wave in Lead IV (Fig. 2). This electrocardiogram was typical of coronary artery disease in the adult.

Impression.—Episodes suggestive of cardiac pain, provoked by the effort of feeding and accompanied by dyspnea, cyanosis, pallor, and sweats, in the presence of an enlarged heart, together with an electrocardiogram showing inversion of T waves in Leads I and II, indicate an inadequate arterial blood supply to the heart muscle and constitute a syndrome strikingly suggestive of the clinical effects produced by anomalous origin of the left coronary artery from the pulmonary artery.

June 20.—Since my preceding visit the distress accompanying feeding had become progressively worse; there was a good deal of wheezing and the paroxysms previously described were occurring even during rest. Examination revealed no new findings, except that the rate of increase in weight was retarded because of the difficulty in feeding; the heart appeared larger than on the previous examination four weeks earlier.

The infant appeared bright, happy, and playful and throughout the examination kept smiling and cooing. But no sooner had the examination been completed than a sudden change came over her. The patient developed an anxious look and her eyes winced sharply as though she was in great pain. She attempted to cry, but the effort apparently added to her agony, and what might have been a crying spell broke up into a succession of short respiratory grunts. She remained immobile. There was dyspnea, tachycardia, cyanosis, and then pallor, resulting in an ashen-gray countenance; perspiration stood out in beads on her forehead.



FIG. 3.



FIG. 4.

Fig. 3.—Right ventricle opened to show the orifice of the anomalous coronary vessel above the posterior cusp of the pulmonary valve. Note the normal appearance of the right ventricular myocardium and endocardium.

Fig. 4.—Left ventricle opened to show the single coronary orifice above the anterior aortic leaflet. The fibrotic appearance of the inner half of the myocardium may be seen. The hypertrophy of the wall and dilatation of the chamber are obvious as is the thickening of the endocardium.

A profound transformation had occurred; the placid infant of only a few minutes before had taken on the expression of a wizened old woman. The attack lasted eight minutes and left the infant completely limp, her entire body covered with cold sweat.

The paroxysm I had just witnessed was similar to those often observed during the acute phase of a coronary attack. There was no question in my mind that my little patient had just experienced a severe attack of cardiac pain.

June 26.—The temperature rose to 101° F.; the patient developed a cough and a nasal discharge. Dr. Shapiro found signs suggesting pneumonia.

June 27.—The temperature rose to 103° F. X-ray examination confirmed the presence of pneumonia. The patient died at 6:45 P.M.

Clinical Diagnosis.—(1) Anomalous origin of the left coronary artery from the pulmonary artery; (2) pneumonia.

Pathologic Findings (by E. R. M.).—A necropsy was performed three hours after death at the Children's Memorial Hospital. The body was that of a moderately well-developed and well-nourished female infant, presenting no notable external abnormalities. On opening the thorax, the heart presented tremendous enlargement to the left and practically obscured the left lung. The right upper lobe was completely atelectatic and the right middle lobe was markedly emphysematous. Patchy areas of pneumonic consolidation were present in the left lung and in the right lower lobe.

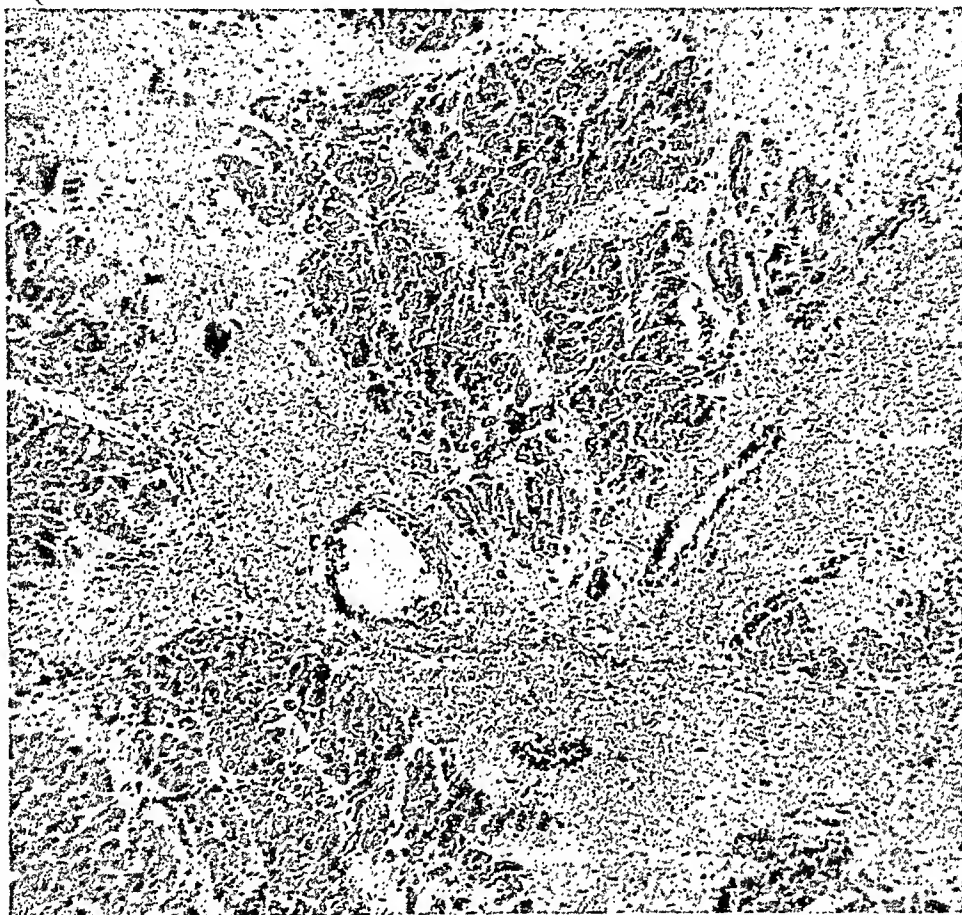


Fig. 5.—Photomicrograph ($\times 100$) of left ventricular myocardium showing extensive fibrosis.

Further examination of the heart revealed dilatation of both ventricles and auricles, but particularly of the left ventricle. The weight was 85.3 grams as compared with an average normal for this age of 27 grams. The measurements of the heart were: mitral valve, 5.1 cm.; aortic valve, 2.8 cm.; tricuspid valve, 5 cm.; pulmonary valve, 4 cm.; left ventricular wall, 0.2 to 0.8 cm.; and right ventricular wall, 0.1 to 0.2 centimeters. The ductus arteriosus was closed. The right coronary artery arose in its usual manner from the sinus of Valsalva of the anterior aortic leaflet and followed the usual course of the normal right coronary artery to supply the right ventricle and a small part of the right border of the left ventricle. No coronary artery orifice was present above the left posterior cusp. The left coronary artery arose from the pulmonary artery in the sinus of Valsalva just above the posterior cusp of the pulmonary valve and thence pursued its normal course to divide into a circumflex branch and an anterior descending branch. This vessel supplied the left ventricle alone as far as could be determined by dissection with fine scissors.

The left ventricle presented hypertrophy of its walls, and on section the inner third of the myocardium was gray and fibrotic in appearance. The chamber was markedly dilated.

The endocardium of the left ventricle was thickened and opaque throughout. The myocardium and endocardium of the right ventricle appeared normal (Figs. 3 and 4).

Histologic examination revealed fairly extensive scarring of the myocardium of the left ventricle, particularly of the inner half, associated with atrophy and vacuolation of the muscle fibers. The endocardium was thickened and fibrotic. No embryonic sinusoids were present.

The smaller coronary artery branches showed slight thickening of the media of the vessel wall by scar tissue, but no endarteritis obliterans was present (Fig. 5).

Other viscera presented no abnormalities.

DISCUSSION

In six of the cases recorded in the literature, individuals with this anomaly have attained adult life. Abbott's⁶ case concerned a woman, 64 years of age, who died accidentally. At autopsy it was found that the descending branch of the left coronary artery expanded into a large sinus, 2 cm. in diameter, which communicated with thick-walled vessels behind it. The most recent record⁷ of an individual reaching adult life was that of a man 30 years of age. Autopsy in this case revealed no myocardial fibrosis, a phenomenon which was attributed to a compensatory arterial supply by the right coronary artery, as demonstrated by a dilatation of the right coronary artery and by accessory distribution of the distal end of the right coronary beyond the interventricular septum and into the ventricular muscle; the area normally supplied by the circumflex branch of the left coronary artery. However, such remarkable anastomoses between the coronary arteries, or between the left coronary artery and the left ventricular cavity, do not occur in the majority of cases with this circulatory defect; death within the first year is therefore the usual outcome. The recognition of this anomaly during life is therefore very important from the point of view of prognosis, so that expectation of life and serious impending consequences may be fully appreciated.

The case here recorded conforms in its clinical features to those presented by the majority of the cases reported. The clinical diagnosis was based on paroxysms of cardiac pain suggesting angina pectoris, marked enlargement of the heart, and an electrocardiogram of the type associated with coronary artery disease. A search of the literature yields very meager information regarding electrocardiographic studies. The only electrocardiogram on record is the one taken by Bland, White, and Garland⁸ in a patient who revealed this circulatory defect at necropsy; the tracing showed a normal axis with inversion of T waves. On the other hand, the electrocardiogram of a patient with idiopathic congenital hypertrophy of the heart⁹ was normal. Full use was made of this information. The electrocardiogram of our patient closely resembled that taken by Bland and his co-workers, and helped considerably in the differential diagnosis.

Pulmonary atelectasis, a feature of this case, has been recorded in other cases and is probably secondary to the hypertrophy and dilatation of the heart. It is worth noting that, consistent with the majority of cases reported, our patient appeared normal at birth. No adequate explanation has thus far been advanced to explain the absence of symptoms during the early weeks of life. One may speculate that the blood supply to the myocardium may be adequate when activity is at a minimum. Another explanation suggested⁸ is that a slight

patency of the ductus arteriosus, which may have escaped occlusion in the early weeks of life, permits a mixture of arterial with venous blood in the pulmonary artery.

SUMMARY

A case is presented of anomalous origin of the left coronary artery from the pulmonary artery in which the condition was diagnosed during life. The diagnosis was made on the following observations: paroxysms of cardiac pain characterized by sweating, pallor, cyanosis, and dyspnea; great enlargement of the heart both clinically and by x-ray examination; and electrocardiograms showing inversion of the T waves in Leads I and II. These constitute a syndrome indicating inadequate arterial blood supply to the heart muscle. The clinical diagnosis was confirmed by necropsy which revealed a left coronary artery arising from the pulmonary artery and supplying the left ventricle alone. No anastomotic coronary circulation existed.

REFERENCES

1. Abrikosoff, A.: Aneurysma des linken Herzventrikels mit abnormer abgangsstelle der linken Karonarterie von der Pulmonalis bei einen funfmonthelien Kinde, *Virchows Arch. f. path. Anat.* 203: 413, 1911.
2. Heitzmann, O.: Drei Seltene Falle von Herzmissbildung, *Virchows Arch. f. path. Anat.* 223: 57, 1917.
3. Sanes, S., and Kenny, F. E.: Anomalous Origin of Left Coronary Artery From the Pulmonary Artery, *Am. J. Dis. Child.* 48: 113, 1934.
4. Soloff, L. A.: Anomalous Coronary Arteries Arising From the Pulmonary Artery, *AM. HEART J.* 24: 118, 1942.
5. Proescher, F., and Baumann, F. W.: Abnormal Origin of Left Coronary Artery With Extensive Cardiac Changes, *J. Pediat.* 25: 344, 1944.
6. Abbott, M. E.: Congenital Heart Disease, *Osler's Modern Medicine*, Philadelphia, 1928, Lea & Febiger, vol. 4.
7. Buddock, J. C., and Stehly, C. C.: Anomalous Origin of Left Coronary Artery From the Pulmonary Artery, *U. S. Nav. M. Bull.* 41: 175, 1943.
8. Bland, E. F., White, P. D., and Garland, J.: Congenital Anomalies of the Coronary Arteries: Report of an Unusual Case Associated With Cardiac Hypertrophy, *AM. HEART J.* 8: 787, 1933.
9. Sprague, H. B., Bland, E. F., and White, P. D.: Congenital Idiopathic Hypertrophy of the Heart, With Unusual Family History, *Am. J. Dis. Child.* 41: 877, 1931.

COMBINED SULFONAMIDE AND DIPHThERIC MYOCARDITIS IN CUTANEOUS DIPHThERIA

RALPH C. GREENE, M.D.
MEMPHIS, TENN.

ALTHOUGH mentioned in all standard works, cutaneous diphtheria with resulting fatal myocarditis is rarely seen in modern practice. Since the onset of this war, only a few reports, not yet prepared for publication, have appeared from military sources. The purpose of this paper is to place on record a case in which the myocardial damage of diphtheria toxin was combined with an inflammatory lesion caused by sulfonamides.

REPORT OF A CASE:

A 21-year-old soldier, who had been in the service for three years, was admitted to our station hospital in England on Nov. 15, 1943, several days after having been transferred from Sicily. He complained of epigastric pain, dark urine, clay colored stools, anorexia, vomiting, and a mild cough. All of these symptoms had been present for one week. Four days after this onset, he developed generalized icterus and the other symptoms abated. He stated that three weeks previously he noticed a lesion having the appearance of a small abrasion approximately $\frac{1}{4}$ inch long on the middle phalanx of the right index finger. This had become larger, until, on admission, it was an elevation $\frac{3}{4}$ inch in diameter and slightly tender. It was covered with epithelium with no break in the skin surface. The patient was not acutely ill. His temperature and pulse were normal. His skin was deeply icteric. The liver could be felt 1 fingerbreadth below the costal margin and was tender. The spleen could not be felt.

The patient was put on routine icterus therapy, consisting of a high-carbohydrate, low-fat, high-vitamin diet with bed rest. A surgical consultation was ordered. After examination, the surgeons reported a spreading infection with lymphangitis, which in several days was tender and palpable. The fluctuant mass was incised and only a thin serous fluid exuded. Hot wet dressings were applied. Two days after incision the patient's temperature rose to 103° F. and the right axillary nodes became more tender and swollen. Despite the administration of 1 Gm. of sulfadiazine every four hours for nine days, the cutaneous lesion did not heal; the adenitis persisted and he continued to run a septic course. On Dec. 1, 1943, two weeks after his admission, and five weeks after the skin lesion was noticed, the patient suddenly developed clonic convulsions and lost consciousness. The pulse was regular and feeble, but the rate was found to be only 17 per minute. The systolic blood pressure

was 70 mm. and the diastolic pressure could not be obtained. In a few minutes he regained consciousness. Although he was rational and oriented, his skin was cold and clammy, he was cyanotic, and the heartbeat continued to be slow.

Electrocardiographic studies revealed an auricular rate of 120 and a ventricular rate of 30. There was complete A-V block. The axis was deviated to the left. The duration of the QRS complex was 0.14 second. The P waves were upright in Lead I and diphasic in Leads II and III. The QRS complexes were slurred in all leads and described as being of the "S" type in Leads I, II, and III. The T waves were upright in the three indirect leads. A chest lead, taken at Position 4, showed an initial upward deflection followed by an inverted T wave.

The smears and cultures of the discharge from the skin lesion revealed diphtheria bacilli, the virulence of which was later confirmed by animal inoculations. The white blood cells were 15,450 with a normal differential count. During the next few days the patient's pulse rate varied between 39 and 60 and the blood pressure was approximately 100/60. Sixty thousand units of diphtheria antitoxin were administered immediately after the diagnosis of diphtheria was made. The patient was given adrenalin and ephedrine in small doses, but he remained extremely weak and cyanotic with cold perspiration and severe nausea. His pulse reverted to a regular rate of 30 two days after the first Stokes-Adams seizure. The first heart sound was noted to be very variable in intensity. Again, during this day he suddenly developed generalized clonic convulsions, became comatose, and expired.

Post-Mortem Findings.—Autopsy, two hours after death, disclosed that the index finger of the right hand was markedly swollen and covered by a bluish mottled discoloration and epidermal desquamation. Over the middle portion of this area was an unhealed incision encrusted with old blood. The axillary lymph nodes were enlarged to pea and almond sizes.

The heart was of normal size and weight with no obvious softness. The myocardium appeared normal on gross examination. The coronary arteries were patent and showed no evidence of sclerosis.

The lungs were crepitant throughout. Some frothy exudation was seen on the cut surface.

The liver was enlarged and about 50 per cent heavier than the normal. It was distinctly darker than usual upon the external and cut surfaces. The hepatic lobulation was increased in distinctness. There were no areas of degeneration or discoloration.

The glands surrounding the anterior fold of the epiploic foramen were greatly enlarged and measured 1 to 2 cm. in diameter. They were soft and elastic in consistency. Their cut surfaces showed an increased prominence of the lymphoid follicles.

The spleen was enlarged to twice its usual size and was firm in consistency. The capsule was tense and of a dark slate blue color. The cut surface showed normal markings. The pulp scraped easily and was dark red and velvety in appearance. The splenic arteries and veins were patent.

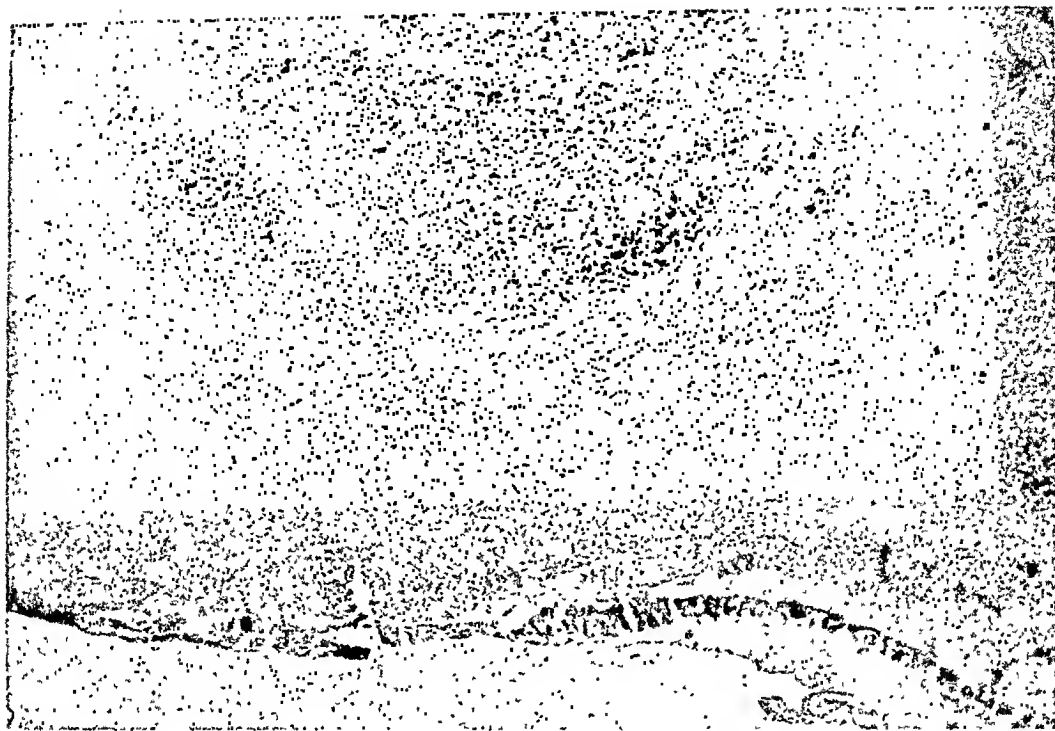


Fig. 1.—Cutaneous lesion showing false membrane and bacterial colonies. (U. S. Army Medical Museum, Negative 87710.)

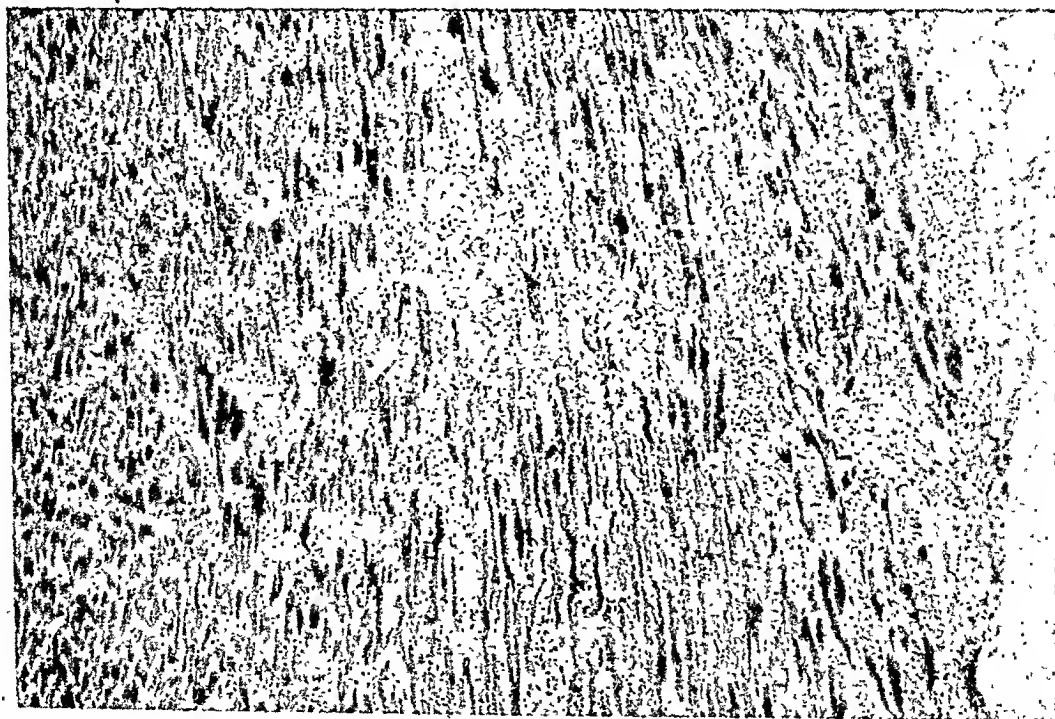


Fig. 2.—Granulomatous interstitial lesions, low power. (U. S. Army Medical Museum, Negative 87713.)

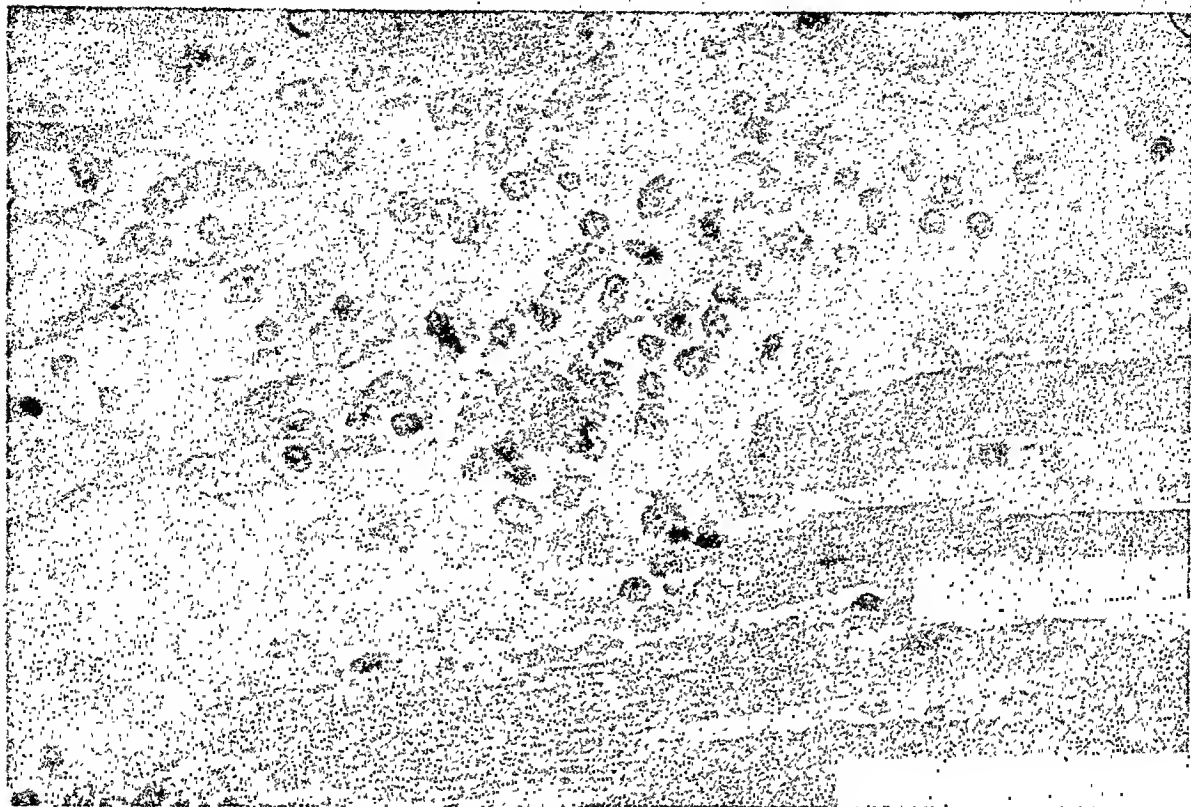


Fig. 3A.—Granulomatous interstitial lesion, high power. Note the large pale mononuclear cells characteristic of "sulfa" medication. (U. S. Army Medical Museum, Negative 87714.)



Fig. 3B.—Myocardial interstitial lesion, high power. The large mononuclear cells are characteristic of sulfonamide myocarditis. (U. S. Army Medical Museum, Negative 87711.)

The mesenteric lymph nodes were enlarged to almond size and in all respects resembled those seen surrounding the bile ducts in the anterior fold of the epiploic foramen.

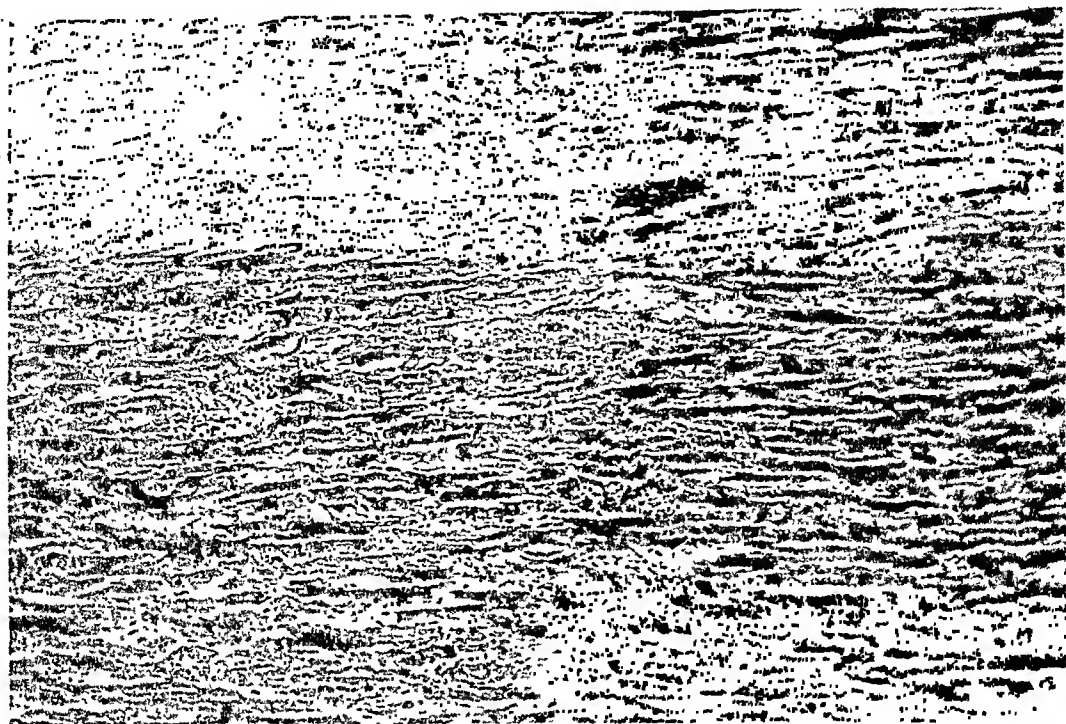


Fig. 4.—Myocardium, showing diffuse lesion with degeneration, fragmentation, and interstitial infiltration. (U. S. Army Medical Museum, Negative 87712.)

Microscopic Observations.—A section through the cutaneous lesion in the right index finger showed ulceration, hemorrhage and an acute inflammatory exudate containing numerous polymorphonuclears. Many collections of blue-staining bacterial colonies could be seen on and near the surface. Under higher power these were revealed to vary in size and to be rod-shaped and transversely banded, with a tendency toward clubbing.

A section through the right ventricle of the heart showed diffuse cloudy swelling. Simple necrosis, Zenker's necrosis and granular degeneration of the myocardium were present in various areas. Many of the cardiac muscle fibers were replaced by new fibrous connective tissue and others were broken up into hyaline masses. The interstitial tissue contained an infiltration of large mononuclear cells with a smaller proportion of polymorphonuclears. Many of these mononuclears were large and pale and contained eosinophilic cytoplasm. Their nuclei were large and vesicular. Section through the wall of the left ventricle revealed a more striking picture with greater necrosis and fragmentation of the heart muscle and the interstitial infiltration being so marked as to constitute a granulomatous lesion.

There were considerable bilateral pulmonary congestion and atelectasis, with mononuclear infiltration and thickening of the alveolar septae. There were numerous pigment-laden macrophages in the alveoli.

The liver sections showed varying degrees of central atrophy and degeneration and considerable congestion of the central vein and sinusoids. The portal spaces contained a heavy infiltration of round cells and polymorphonuclear leucocytes.

The germinal centers of the spleen showed enlargement and early focal necrosis. There was a reticulo-endothelial proliferation in the follicles. The splenic sinusoids were dilated and congested with red blood cells. The enlarged lymph nodes also showed reticulo-endothelial hyperplasia in the germinal centers as well as in the intervening medullary cords. Many polymorphonuclears were present in the sinusoids.

The anatomic diagnoses were: cutaneous diphtheria and wound of the right index finger; acute diphtheritic and sulfonamide myocarditis; acute infectious hepatitis; pulmonary edema and atelectasis; acute toxic mesenteric lymphadenitis; and chronic passive congestion of liver and spleen.

COMMENT

Chin and Huang,¹ in their definitive review of the literature, report that the majority of investigators of diphtheritic myocarditis find mainly an involvement of the cardiac parenchyma. Others, however, report an interstitial inflammation. There is no united opinion regarding the sequence of these changes. Most consider the interstitial changes to be a reaction secondary to the parenchymatous lesion, with the inflammatory cellular reaction and connective tissue proliferation limited to areas where the myocardium is undergoing necrosis. Cases, however, have been reported of independent interstitial inflammation, unassociated with a parenchymatous lesion.^{4, 5}

Burkhardt, Eggleston, and Smith,² who studied 140 cases of diphtheritic myocarditis, found that 28 had electrocardiographic changes. Fourteen of these died, even though large doses of antitoxin were administered, on or before the fourth day of illness. All of these patients had conduction changes, eleven being auriculoventricular dissociation. Only three patients with conduction changes survived, and all with auriculoventricular dissociation succumbed. They report histologic changes progressing through edema, congestion, cellular infiltration, degenerative changes and fibrosis.

A new type of interstitial myocarditis, has been reported recently by French and Weller.³ They found that out of 283 patients who received large quantities of sulfonamides and later came to necropsy, 126 had myocarditis. There was a perivascular and diffuse infiltration with large elastofibrous mononuclears and other cells with granular acidophilic cytoplasm. A similar type of myocarditis was experimentally produced by them in rats and mice.

In a series of 51 cases of diphtheria occurring consecutively among German Prisoners of War from North Africa, seven developed myocarditis. Only four had cutaneous diphtheria and one of these had involvement of the myocardium. All of the patients with cardiac signs had received sulfonamides, and all recovered.

SUMMARY

A study of this case history with its pathologic findings leads to the conclusion that the myocardial changes were due to a combination of sulfonamides and diphtheria toxin. The original lesion was not characteristic of wound diphtheritis,⁹ as it was covered by epithelium and was phlegmonous in character. One must presume that the *Bacillus diphtheriae* was a secondary invader introduced perhaps during the surgical intervention, as suggested by a personal communication from Dr. C. V. Weller, who feels that such an atypical lesion could be explained in this manner.

The cloudy swelling, simple necrosis, and granular fragmentation of the myocardium is characteristic of diphtheritic myocarditis. In part, the interstitial reaction, the round cell and polymorphonuclear infiltrations, and the fibroblastic proliferation are subsidiary to these diphtheritic effects. It is certain, however, that additional changes in kind and degree were induced by sulfonamide medication; the large pale mononuclear cells with eosinophilic cytoplasm are considered to be representative. It is not, however, possible to assess accurately the added influence of the lesion produced by the drug in causing the fatal termination.

The impression remains that the usual hazards of sulfonamide therapy are increased when the heart is already damaged by diphtheria or other toxins. In the course of such treatment it is necessary to evaluate, at frequent intervals the state of the cardiovascular system as well as to limit medication to the quantity consistent with favorable results.

REFERENCES

1. Chin, K. Y., and Huang, C. H.: Myocardial Necrosis in Diphtheria With a General Review of the Lesions of the Myocardium in Diphtheria, *AM. HEART J.* 22: 690, 1941.
2. Burkhardt, E. A., Eggleston, C., and Smith, L. W.: Electrocardiographic Changes and Peripheral Nerve Palsies in Toxic Diphtheria, *Am. J. M. Sc.* 195: 301, 1938.
3. French, A. J., and Weller, C. V.: Interstitial Myocarditis Following Clinical and Experimental Use of Sulfonamide Drugs, *Am. J. Path.* 18: 109, 1942.
4. Neubauer, C.: Diphtheritic Heart Disorders in Children, *Brit. M. J.* 2: 89, 1942.
5. Bramwell, C., and King, J. T.: Principles and Practices of Cardiology, London, 1942, Oxford University Press, p. 476.
6. Saffron, M. H.: Cutaneous Diphtheria as Military Problem; Review of Literature With Report of Case, *Arch. Dermat. & Syph.* 51: 337, 1945.
7. Rapport, H. M.: Desert Sores, *Brit. M. J.* 2: 96, 1942.
8. Bull. U. S. Army M. Dept. 3: 21, 1944.
9. Fleck, S., Kellam, J. W., and Klippen, A. J.: Diphtheria Among German Prisoners of War, *Bull. U. S. Army M. Dept.* 3: 80, 1944.

PAROXYSMAL VENTRICULAR TACHYCARDIA FOLLOWED BY ELECTROCARDIOGRAPHIC SYNDROME

WITH A REPORT OF A CASE

LIEUTENANT COLONEL LESLIE B. SMITH, M.C.
ARMY OF THE UNITED STATES

STRIKING electrocardiographic alterations may persist for a long period of time after an attack of paroxysmal tachycardia in individuals who do not have evidence of structural heart disease. These changes are most prominent following paroxysms of ventricular tachycardia and consist of depression of the S-T segments, lowering or inversion of the T waves, and prolongation of the Q-T interval. This phenomenon has not been generally recognized.

Graybiel and White¹ (1934) were probably the first to call attention to the fact that there may be an inversion of T waves which gradually return to normal following paroxysmal tachycardia in individuals who do not have other evidences of heart disease. Burak and Scherf² (1933) reported that after an attack of persistent paroxysmal tachycardia the electrocardiogram may for several hours show negative T waves, lowered S-T segment, and alterations of the initial deflections.

These electrocardiographic changes may be misinterpreted as indicative of serious heart diseases, such as coronary occlusion, coronary thrombosis, myocardial strain, cardiac damage caused by the tachycardia (anoxia, exhaustion), toxic myocarditis, and pericarditis; or the changes may be ascribed to quinidine or digitalis intoxication.

The only review of this subject to date was that of Cossio, Vedoya, and Berensky,³ which appeared in the Argentine literature. They discussed their findings after analyzing twenty-two cases. It is the purpose of this paper to supplement their discussion, cite the three cases subsequently reported by Zimmerman,⁴ and report an additional case.

CASE REPORT

First Admission.—A 23-year-old man of Mexican and Indian extraction was admitted to the hospital on Oct. 6, 1944, complaining of a head cold and cough of four days' duration.

He did not recall having had any illness in the past, even in childhood. Closer questioning revealed that five years previously he had an attack of "gas on my stomach which pushed up on my heart and tended to shut off my wind. This spell lasted only a few hours and stopped suddenly after the doctor gave me some white medicine." During the previous three years he had had two similar attacks, each lasting ten minutes.

The present illness began four days before admission with a "head cold" and a little sore throat and cough, which did not interfere with his participation in the rigorous military training. The morning before, while engaged in strenuous physical activity, he

Received for publication Aug. 27, 1945.

experienced a burning sensation across the front of his chest which was aggravated by deep breathing and coughing. He felt weak and shaky and noted chilly sensations, headache, and malaise.

At the time of admission the patient was comfortable and did not appear to be very ill. The temperature was 101.2° F., the apical heart rate was approximately 190 per minute, and the blood pressure was 90/70. There were numerous asthmaticoid râles heard in the bases of both lungs, with a few moist râles in the left base. There were no other abnormal physical findings. The leucocyte count was 15,780 per cubic millimeter with 75 per cent polymorphonuclears cells. An x-ray film of the chest revealed a moderate-sized area of pneumonia in the medial portion of the right lower lobe. An electrocardiogram (Fig 1, A) showed a ventricular tachycardia with a ventricular rate of 159 and an auricular rate of 80 per minute. The duration of the QRS complex was 0.10 to 0.11 second; all of the limb leads showed deep and slurred S waves. The only major deflection in CF_1 was upright.

The temperature was normal four hours after admission and was not significantly elevated during the remainder of the illness.

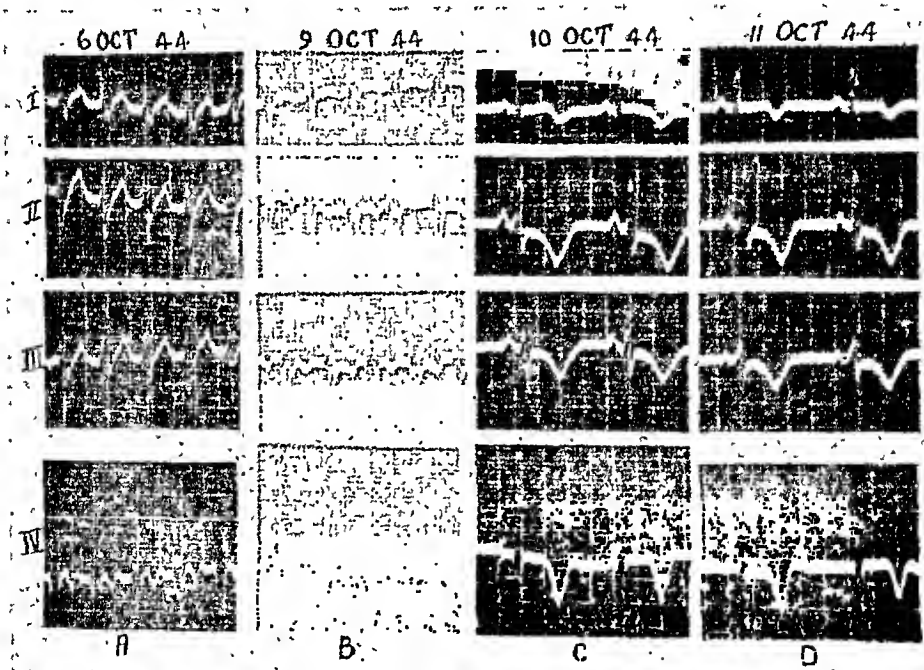


Fig. 1.—Serial electrocardiograms made during first hospital admission. See text for description.

Repeated attempts to stop the tachycardia by ocular pressure and massage of the carotid sinuses were unsuccessful. A test dose of 2 grains of quinidine sulfate was given. He was then given 4 grains of quinidine sulfate every three hours for four doses.

The second day the tachycardia persisted and the dose of quinidine was increased to 6 grains every two hours for an additional five doses. Then 10 c.c. of calcium gluconate were given intravenously without affecting the heart rate. The electrocardiogram was essentially unchanged. Type 32 pneumococci were found in the sputum. Asthmaticoid râles were present in the chest, but there were no other abnormal physical findings. These findings remained unchanged during the third day. Because of the pneumonitis and the tachycardia the patient was placed in an oxygen tent.

During the fourth day he complained of smothering sensations and inability to get his breath. He became less dyspneic in an oxygen tent. There was moderate distention of the neck veins. Early in the day the left lobe of the liver was found to be enlarged and tender, and several hours later the right lobe had become palpable and tender. The pulse

rate remained approximately 160 per minute and the blood pressure was 86/70. Quinidine therapy was again instituted in doses of 6 grains every hour for four doses, then 6 grains every two hours. After the third dose of quinidine, $\frac{1}{4}$ grain of morphine sulfate was given. This medication was supplemented with 4 drams of ipecac, which induced vomiting without altering the heart rate. Electrocardiograms (Fig. 1, *B*) made this day showed a ventricular rate of 162 per minute, an auricular rate of 80 per minute, a QRS interval of 0.12 second, deep and slurred S waves in the limb leads, and inversion of the T waves in Leads II, III, and IV.

The next morning the pulse rate was 154 per minute, and thirty minutes later the rate was 84 per minute. Seventy-eight grains of quinidine sulfate were given during the twenty-four-hour period preceding the change to normal rhythm. An electrocardiogram (Fig. 1, *C*) recorded approximately thirty minutes after cessation of the tachycardia showed a QRS interval of 0.08 second, marked depression of the S-T segments in Leads II and III, wide and deeply inverted T waves in the limb and precordial leads, and a Q-T interval of 0.558 second. Another electrocardiogram taken three hours later was essentially the same. During the first day of normal rhythm, the patient was no longer dyspneic and there was a marked clearing of the râles in both lungs. Quinidine medication was discontinued for six hours, then $1\frac{1}{2}$ grains were given every four hours for seven doses.

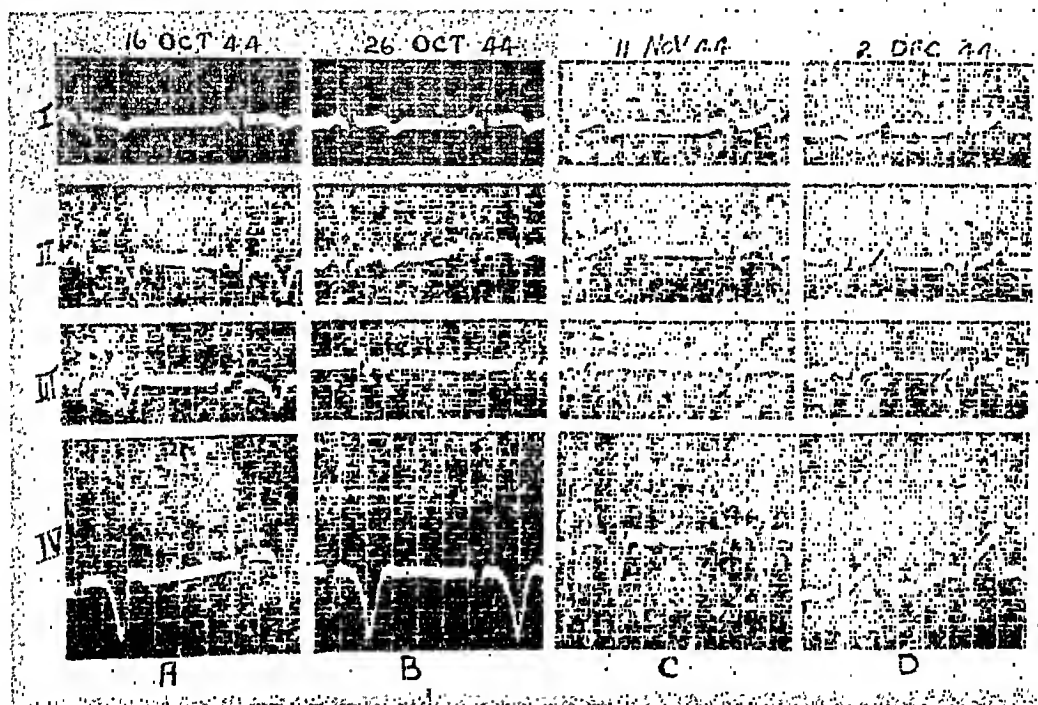


Fig. 2.—Serial electrocardiograms made during first hospital admission. See text for description.

The next day he complained of a mild headache, right earache, and deafness in the right ear. The liver was no longer enlarged or tender. The temperature was normal and the leucocyte count was 10,000 per cubic centimeter with 80 per cent polymorphonuclear cells. There was some injection of the right eardrum, and sulfadiazine was given in 1 Gm. doses every four hours for nine days. A diagnosis of nonsuppurative otitis media was made. These symptoms subsided rapidly, and the temperature remained normal.

On the eleventh day a roentgenogram showed almost complete clearing of the pneumonic process. The patient continued to be free of symptoms, and the physical examination revealed no abnormal findings. Because of our uncertainty as to the significance of the electrocardiographic changes, he was kept in bed until the twenty-first day, when graduated exercises were begun. At this time the electrocardiogram (Fig. 2, *B*) showed diphasic T_1 , T_2 , and T_3 and deep inversion of T_4 .

The convalescence continued to be uneventful, and physical findings were normal except for persistence of coarse râles in the base of the right lung. Frequent examination failed to elicit a friction rub or cardiac murmurs. A teleroentgenogram on the nineteenth day and a fluoroscopic examination on the sixty-fifth day were normal. He was transferred to the rehabilitation facility on the seventy-first day, where he remained asymptomatic. One hundred five days after admission, electrocardiograms made immediately after one and one-half minutes of stationary running, and thereafter at intervals of five, ten, fifteen, and twenty minutes, showed no changes in any portion of the complexes.

Second Admission.—Following the first admission he did duty as a cook, working twenty-four-hour shifts with twenty-four hours off duty between the shifts. He stated that he had felt well, and that the work did not fatigue him.

Fifteen hours prior to this admission, following the consumption of a "large amount of beer and a few whiskies," he noted a sudden onset of a burning sensation in the region of the sternum, a slight choking sensation at the base of his neck, and a pulse rate which he said was too fast to count. He had slept poorly that night, but reported for duty at 4:30 A.M. In about six hours he became too weak to continue his duties and was sent to the hospital.

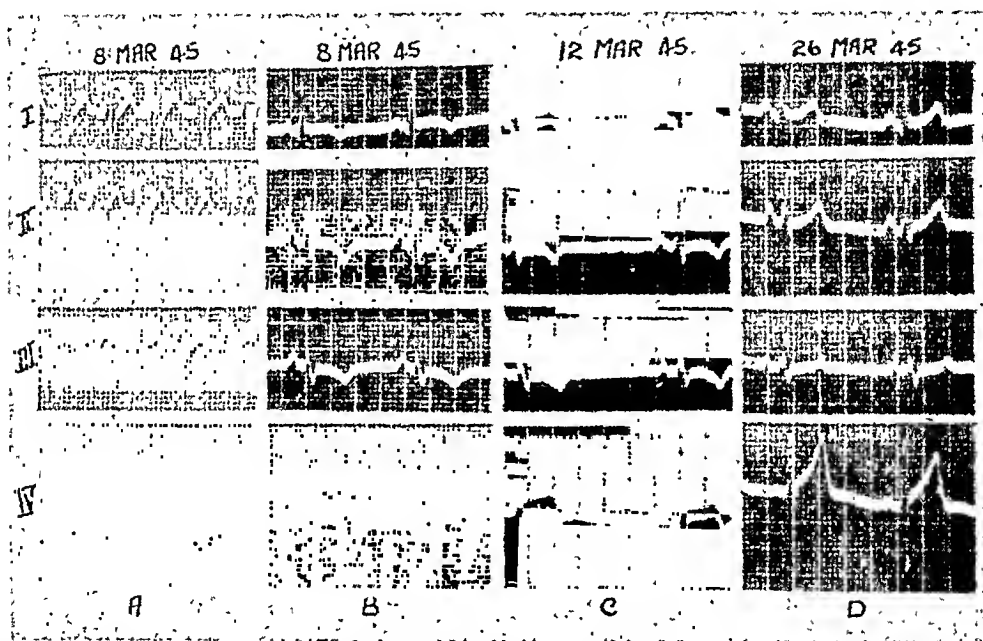


Fig. 3.—Serial electrocardiograms made during second hospital admission. The tracings are described in the text.

At the time of admission he complained only of a mild burning sensation, located under the sternum, and a slight choking sensation. Examination revealed an irregular pulse with a rate of 170 per minute, with a tic-tac rhythm heard at the apex. The blood pressure was 94/80. There were no other abnormal findings. An electrocardiogram (Fig. 3, A) revealed a ventricular tachycardia with a ventricular rate of 150 per minute and an auricular rate of 98 per minute. The complexes were virtually the same as those during the first attack, and showed the deep and slurred S waves in all limb leads. He was aware that his heart rate had returned to normal following six hours of quinidine medication, during which time he received 19½ grains. An electrocardiogram (Fig. 3, B) taken two hours after the return of normal rhythm showed a diphasic T_1 , inverted T_2 , T_3 , and T_4 , slight elevation of $S-T_1$ and $S-T_4$, and a depression of $S-T_2$, and $S-T_3$.

The patient felt perfectly well during this stay in the hospital. He was kept at bed rest for four days. There were no evidences of heart disease or of other abnormal find-

ings. The blood counts, urinalysis, and sedimentation rates were normal. There was a gradual evolution of the electrocardiogram (Fig. 3) to normal on the fifteenth day, and the patient was returned to limited duty.

Third Admission.—He had been well since the last admission except that on two occasions, two months and one month before, he had noted periods of burning in the left side of the chest, with irregular heart action lasting one and one-half to two hours.

At 11:00 A.M. on the day before admission he noted a burning sensation, which he located at the level of the xiphoid process, and was aware of an irregular and fast heart action. There were no unusual circumstances preceding this attack. At the time of admission his complaints were minimal, and there were no abnormal physical findings except the tachycardia. The ventricular rate was 160 and the blood pressure was 90/70. The leucocyte count, urinalysis, and blood sedimentation rates were normal. An electrocardiogram (Fig. 4, A) showed ventricular tachycardia with a ventricular rate of 160 per minute and an auricular rate of 80 per minute. This attack terminated spontaneously after a total duration

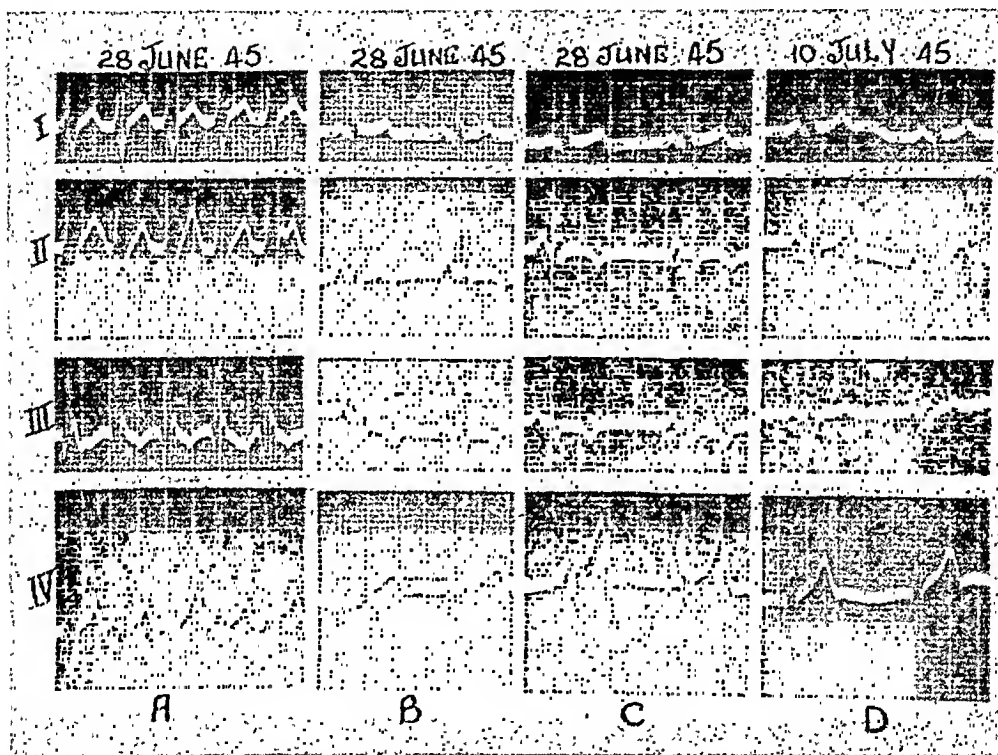


Fig. 4.—Serial electrocardiograms made during the third hospital admission. The tracings are described in the text. There is a reversal of polarity in Lead III of tracing A.

of twenty-four hours. An electrocardiogram (Fig 4, B) taken one hour after the return of normal rhythm showed slight elevation of S-T₁ and S-T₂, depression of S-T₃, with inversion of T₂ and T₃. This electrocardiogram resembles that of a posterior infarction. The next day (Fig 4, C) the elevation of S-T₁ and S-T₂ was not as prominent, and the T-wave inversions were deeper. Two days later the T-wave inversions were less prominent; on the eighth day the T waves were all upright, and on the thirteenth day the voltage of the T waves was normal. The temperature, the leucocyte count, and the blood sedimentation rate during this admission remained normal, and the patient was discharged to limited duty on the fourteenth day.

Ten days after the third admission he had an attack which lasted two hours. Electrocardiograms taken the following day and three days later were normal. A teleroentgenogram was normal.

Case Summary.—A 23-year-old man was admitted to the hospital three times during attacks of ventricular tachycardia. The past history disclosed that during the previous five years he had symptoms which in view of the present findings were interpreted to represent three short attacks of paroxysmal tachycardia. The first attack observed by us lasted four days. This attack was associated with a "cold" and pneumonitis, which was diagnosed as mild atypical pneumonia, etiology undetermined. During the fourth day of this attack there was definite evidence of heart failure which cleared promptly following the cessation of the paroxysm. Seventy-eight grains of quinidine sulfate were administered during the twenty-four-hour period preceding the termination of the ninety-six-hour paroxysm. There were no evidences of structural heart disease.

The posttachycardial electrocardiographic manifestations were of unusual interest. After the cessation of the attack the T waves were deeply inverted in all leads, with depression of the S-T segment in Leads II and III and prolongation of the Q-T interval. At first these changes were thought possibly to represent quinidine intoxication; however, these abnormalities persisted long after the action of quinidine had subsided. Serial electrocardiograms (Figs. 1 and 2) showed persistence of the abnormal changes, with a gradual return to normal in fifty-seven days. The patient felt well during the period of observation, except during the fourth day when heart failure was present and during the days of catarrhal otitis media. At no time after the cessation of the tachycardia were there any abnormal cardiac findings, and the laboratory findings were normal. Although the clinical findings did not substantiate a diagnosis of structural heart disease, various diagnostic impressions were offered by observers and reviewers. These included myocardial infarction or decrease in circulation due to obstruction in a possible anomalous coronary system⁵ and toxic changes in the myocardium secondary to acute infection.⁶ The author, at first, was of the opinion that the electrocardiographic manifestations, although atypical, were due to a pericarditis associated with the pneumonic process in the left lower lobe. A definite final diagnosis was not established, but it was decided at the time of discharge that structural heart disease was not present.

The second paroxysm of tachycardia, which lasted twenty-one hours, was possibly precipitated by alcoholic excess. The posttachycardial changes were not as marked as during the first attack and returned to normal more rapidly (fifteen days). The patient had had two short paroxysms between the second and third admission. The third observed attack of ventricular tachycardia lasted twenty-six hours before it terminated, spontaneously. The electrocardiographic changes this time did not include depression of S-T₂ and S-T₃ or negativity of T₁, and there was a return to normal in twelve days.

It is thought that this series of electrocardiograms are representative of a postparoxysmal ventricular tachycardial syndrome. The sequence of the electrocardiographic changes are in keeping with the postulates of Cossio, Vedoya, and Bereonsky.³ Figs. 1 and 2 show a ventricular tachycardia with deep and slurred S waves in the limb leads. This would indicate an automatic ventricular focus located some place in the lateral portion of the left ventricle giving rise to a post-

tachycardial electrocardiogram of predominant T_3 (T_3 and T_2) type with some negativity of T_1 . Fig. 2 is of the same T_3 type, but has less prominent T_1 changes, which may indicate that the focus was more posterior. The T waves in Lead I are positive in the posttachycardial electrocardiograms (Fig. 4) taken after the third attack. These electrocardiograms may be interpreted as indicating that the focus was more posterior than it was during the previous two attacks.

The difference in the degree of the changes in the three series of electrocardiograms is probably not directly related to the duration of the paroxysm. The duration of the third paroxysm showing no T_1 or T_4 changes was longer, twenty-six hours, than that of the second paroxysm, twenty-one hours, in which T_1 was definitely negative.

DISCUSSION

The electrocardiographic syndrome following paroxysmal tachycardia consists of changes in (1) the T waves, (2) the S-T segments, and (3) the duration of the Q-T interval. The most characteristic T waves are those which are deeply inverted, with a broad base and almost equal limbs. However, these may vary in degree from simple reduction in voltage to varying depths of inversion of the T waves. These changes may be present in all three limb leads, Lead I or Leads I and II (T_1 type), or Lead III or Leads II and III (T_3 type). Negative T waves in all three limb leads was a predominant finding in two of the twenty-two cases previously reviewed,³ and in the author's case (Fig. 1).

The S-T segments are usually depressed in one or more leads (Fig. 1, B). These S-T depressions are most prominent in the same leads which have the most marked T-wave inversions. Another feature is that the T-wave changes usually persist for a long period: six to sixty days.^{4, 7} A slight reciprocal elevation of the S-T segment in the opposite limb lead may occasionally be present (Fig. 4, B). Prolongation of the Q-T interval is common.

Although paroxysmal tachycardias of auricular origin occur more than ten times,^{3, 8} as frequently as those of ventricular origin, only two cases of pure auricular paroxysmal tachycardia have been reported in which there were some alterations in the posttachycardial electrocardiograms. In one of these two cases, that reported by Zimmerman,⁴ the T-wave changes were minimal; there were no depressions in the S-T segments, and the abnormality lasted less than two days. Two of the other six reported cases of supraventricular origin had aberrant ventricular complexes, and the other four cases showed the Wolf-Parkinson-White syndrome. There are now nineteen cases on record in which this syndrome followed paroxysmal ventricular tachycardia. These electrocardiographic manifestations seem to occur so infrequently following auricular paroxysmal tachycardia, and the magnitude of the changes are so much less that it seems justifiable to state that these alterations of the electrocardiogram constitute a characteristic electrocardiographic syndrome which may be present following paroxysmal ventricular tachycardia.

At the present time it cannot be determined how frequently this syndrome follows ventricular tachycardia. However, there are a number of published electrocardiograms made following attacks of ventricular tachycardia which show otherwise unexplained changes similar to those under discussion.⁹⁻¹²

That this syndrome is more related to the ventricular structures than to the supraventricular structures is emphasized by the correlation between the contour of the electrocardiogram during the attack of paroxysmal ventricular tachycardia and the pattern which follows the tachycardia. From an analysis of the precordial leads in one of their cases, Cossio, Vedoya, and Berconsky³ thought that the sequence of disappearance of the negative T waves were expressions of a localized myocardial disorder. They found that in all of the six cases with left axis deviation during ventricular tachycardia and two cases of supraventricular tachycardia with aberrant ventricular complex there was a T_3 type (negative T_3 or negative T_2 and T_3) of posttachycardia electrocardiogram. The two additional cases of ventricular tachycardia reported by Zimmerman⁴ showed left axis deviation during the paroxysm and the T_3 type of pattern following the attacks. All three cases of ventricular tachycardia with right axis deviation during the attack had T_1 types (negative T_1 or T_1 and T_2) following the paroxysm.

Four of the collected cases³ and the author's case (Figs. 1, A, 3, A, and 4, A) showed wide notched S_1 waves with deep shurred S_2 and S_3 waves and the T_3 type of posttachycardial electrocardiogram. Four of these cases showed some negativity of T_1 . The author's case (Fig. 1, C), besides deep inversions of T_2 and T_3 , showed a deep inversion of T_1 two hours after termination of the four-day paroxysm. Fig. 3, B, shows a smaller negativity of T_1 after the attack of twenty-one hours' duration, and a positive T_1 (Fig. 4, B) after an attack of twenty-six hours' duration. These cases represent combined T_1 and T_3 types, excepting the tracing shown in Fig. 4, B. Cossio and his co-workers³ postulated that in this group the ectopic focus is situated on the posterior or posterior lateral portion of the left ventricle rather than on the anterior face, and that the T_3 type should be expected with a negative T_1 which will be of more prominence the nearer the focus is to the anterior surface. If this hypothesis is true, the electrocardiograms recorded in the author's case represent different active foci during each of the attacks: Fig. 1, C, shows the most anteriorly located focus and Fig. 4, B, shows a more posteriorly located focus. In all the sixteen cases of ventricular tachycardia studied, the posttachycardial electrocardiographic pattern could be determined by the QRS complexes present during the attack.

These findings support the contention of Cossio, Vedoya, and Berconsky³ that from the contours of the electrocardiogram during the attack of paroxysmal tachycardia, especially in the ventricular type, the automatic ectopic focus which originates the tachycardia can be located and the type of posttachycardial electrocardiographic configuration can be predicted.

Although the validity of this concept may be questionable, the frequency with which the posttachycardial pattern can be predicted by the contour of the QRS during the paroxysm is probably more than a coincidence.

Geiger¹⁵ first called attention to the occurrence of a prolongation of the Q-T interval following paroxysmal tachycardia. In his case, the Basett index (K) was 0.509 and 0.535 (normal, 0.392). Cossio and his associates found that in nine cases K varied from 0.45 to 0.60 with an average of 0.516. In the author's case the average K during the first day following a four-day paroxysm was 0.558; however, K equaled only 0.387 following an attack of twenty-four hours' duration.

The mechanism of production of the posttachycardial pattern is not known. Various authors have offered theoretical explanations, such as cardiac insufficiency¹¹; fatigue and exhaustion of the myocardium resulting from the prolonged attacks of tachycardia¹³; overload of the myocardium connected with the duration of the attack¹⁴; myocardial ischemia associated with a sharply diminished cardiac output during the many hours of high ventricular rate, producing a reversible injury¹⁵; modification of a chemical or other nature of the myocardium⁷; cardiac damage caused by the tachycardia (anoxia, exhaustion)¹⁶; and occult coronary sclerosis. These theories all postulate some disproportion between the blood supply and the work of the heart or some type of structural damage. That these conditions exist as the cause of the posttachycardial electrocardiographic alterations is hardly tenable for the following reasons: the attacks of auricular tachycardia may persist for weeks without producing these electrocardiographic changes; the syndrome almost always follows paroxysmal ventricular tachycardia; the duration of the ventricular tachycardia is not directly related to the posttachycardial electrocardiographic changes, as they may occur after attacks as brief as three hours¹⁴; the electrocardiographic changes may persist for long periods (two months) unassociated with impaired cardiac function; and the syndrome may be repeatedly shown in the same patient without evidence of structural heart disease.

Two cases which came to autopsy³ did not have demonstrable heart disease, and only three^{3, 4} of the twenty-six cases now cited were thought to have clinical heart disease; hence, it does not seem likely that organic heart disease plays a significant role in the production of the posttachycardial syndrome.

The most plausible explanation³ is that the localized automatic focus, which is responsible for the paroxysmal tachycardia, retains gradually diminishing activity which causes the posttachycardial electrocardiographic changes.

CONCLUSIONS

1. A case is reported of a patient without structural heart disease whose electrocardiograms are examples of a postparoxysmal ventricular electrocardiographic syndrome.

2. The postparoxysmal ventricular syndrome is characterized by inversion of the T waves in one or more leads, with depression of the S-T segments in the leads where the T-wave inversions are the most prominent, and by prolongation of the Q-T interval.

3. The type of the postventricular tachycardial manifestations can be predicted from the QRS components which are present during the paroxysm of

ventricular tachycardia. When left axis deviation is present during the paroxysm, it may be assumed that an automatic focus is active in the right ventricle and predicted that the posttachycardial pattern will be a T_3 type (negative T_3 or negative T_2 and T_3). When right axis deviation is present during the tachycardia, the focus is probably in the left ventricle and the posttachycardial electrocardiograms will be the T_1 type (negative T_1 and T_2). In those cases where slurred and deep S waves are prominent during the paroxysm, it is assumed that the automatic focus is in the left lateral portion of the heart and that a combination of T_1 and T_3 types will follow, with the negativity of T_1 most marked when the focus is more anteriorly located.

4. As postulated by Cossio, Vedoya, and Bereonsky,³ it is thought that the automatic focus which is responsible for the paroxysmal ventricular tachycardia retains some type of activity after the cessation of the tachycardia, influencing the electrical phenomenon to produce the abnormalities of the T waves, S-T segments, and the Q-T intervals.

5. This syndrome is not indicative of serious heart disease, for which it may be mistaken.

REFERENCES

1. Graybiel, A., and White, P. D.: Inversion of the T Wave in Lead I or II of the Electrocardiogram in Young Individuals With Neurocirculatory Asthenia, With Thyrotoxicosis, in Relation to Certain Infections, and Following Paroxysmal Tachycardia, *AM. HEART J.* 10: 345, 1934.
2. Burak, M., and Scherf, D.: Quoted from Scherf, D., and Boyd, L. J.: *Clinical Electrocardiography*, ed. 2, St. Louis, 1941, The C. V. Mosby Co., p. 138.
3. Cossio, P., Vedoya, R., and Bereonsky, I.: Modifications of the Electrocardiogram Following Certain Attacks of Paroxysmal Tachycardia, *Rev. argent. de cardiol.* 11: 164, 1944.
4. Zimmerman, S. L.: Transient T Wave Inversion Following Paroxysmal Tachycardia, *J. Lab. & Clin. Med.* 29: 598, 1944.
5. Herrmann, G.: Personal communications, October, 1944, and January, 1945.
6. Barnes, A. R.: Personal communications, December, 1944.
7. Campbell, M.: Inversion of T Waves After Long Paroxysms of Tachycardia, *Brit. Heart J.* 4: 49, 1942.
8. Palmer, R. S., and White, P. D.: Paroxysmal Ventricular Tachycardia With Rhythmic Alternation in Direction of the Ventricular Complexes, *AM. HEART J.* 3: 454, 1928.
9. Riseman, J. E. F., and Linenthal, H.: Paroxysmal Ventricular Tachycardia, *AM. HEART J.* 22: 219, 1941.
10. Williams, C., and Ellis, L. B.: Ventricular Tachycardia, *Arch. Int. Med.* 71: 137, 1943.
11. Campbell, M., and Elliott, G. A.: Paroxysmal Tachycardia; Etiology and Prognosis of One Hundred Cases, *Brit. M. J.* 1: 123, 1939.
12. Cooke, W. T., and White, P. D.: Paroxysmal Tachycardia, *Brit. Heart J.* 5: 33, 1943.
13. Dubbs, A. W., and Parmet, D. H.: Ventricular Tachycardia Stopped on the Twenty-First Day by Giving Quinidine Sulfate Intravenously, *AM. HEART J.* 24: 272, 1942.
14. Currie, G. M.: Transient Inverted T Waves After Paroxysmal Tachycardia, *Brit. Heart J.* 4: 149, 1942.
15. Geiger, A. J.: Electrocardiograms Simulating Those of Coronary Thrombosis After Cessation of Paroxysmal Tachycardia, *AM. HEART J.* 26: 555, 1943.
16. Scherf, D.: Alterations in the Form of the T Waves With Changes in Heart Rate, *AM. HEART J.* 28: 332, 1944.

Abstracts and Reviews

Selected Abstracts

Russek, H. I., Southworth, J. L., and Zohman, B. L.: Selection of the Hypertensive Patient for Sympathectomy. *J. A. M. A.* 130: 927 (April 6) 1946.

In view of the increasing frequency with which sympathectomy is being performed in the treatment of hypertension, it becomes of growing importance to develop an accurate means by which favorable cases may be selected. Sodium nitrite, sodium amytal, and cold pressor tests, while still widely used, have not proved to be entirely satisfactory. While high spinal anesthesia appears to yield some information in the determination of favorable patients for operation, it introduces various factors which give misleading results. Thus the loss of muscle tone and complete motor paralysis observed in the lower part of the body in spinal anesthesia may, of themselves, materially affect the height of the blood pressure through the medium of venous stasis, diminished venous return to the heart, and fall in cardiac output. The hemodynamic response to this procedure does not seem comparable to that following surgical sympathectomy.

The use of caudal anesthesia is suggested as a means of selecting hypertensive patients for surgery. The following are some of the advantages of continuous caudal anesthesia: (1) muscle tone and motor power of the lower extremities are little affected; (2) respiration is essentially unchanged; and (3) the height of anesthesia is easily and safely raised to the desired level by repeated small injections. These authors maintain that by gradual and progressive block of sympathetic nerve segments from below upward, a clear concept may be obtained concerning the degree of neurogenic influence and extent of surgery indicated in the given case. They give a dose which suffices to cause a gradual rise in the level of skin anesthesia in the sixth thoracic segment. By this method they were able to lower the blood pressure of hypertensives to normal in 42 of 60 patients. By levels of anesthesia varying from the tenth to the fourth thoracic segment, they were able to accurately predict the outcome of surgical sympathectomy in 11 of 12 patients, whereas other tests were found unreliable when employed for this purpose. BELLET.

Lian, C.: Cardio-Esophageal Auscultation. *Arch. d. mal. du cœur.* 38: 221 (Sept.-Oct.) 1945.

The author's technique of esophageal auscultation is to pass a Faucher gastric lavage tube, or preferably an Einhorn tube, into the esophagus and to attach the ear pieces of a binaural stethoscope to its outer end. Cardiac auscultation was performed by this means in a series of twenty-six patients. In three patients, auscultation was unsatisfactory because of nausea. It is reported that valvular murmurs of all types as well as the heart sounds can be clearly heard when the breath is held during inspiration and expiration. The murmur which is best heard is that of mitral insufficiency because it presumably arises from the left auricle which is in close approximation to the esophagus.

Attention is called to the value of esophageal auscultation in the diagnosis of mitral insufficiency. The author states that if no murmur is audible when the end of the tube is at a level 20 to 40 cm. below the dental arch, the conclusion is warranted that there is no insufficiency of the mitral valve.

An auricular presystolic sound was very rarely audible by esophageal auscultation in normal subjects. This observation supports the view that the presystolic auricular sound

which appears on phonocardiograms is actually exceptional as an audible phenomenon in normal subjects in contrast to the frequency with which the physiologic third sound is heard.

LAPLACE.

Cotlove, E., and Vorzimer, J. J.: Serial Prothrombin Estimations in Cardiac Patients; Diagnostic and Therapeutic Indications, Use of Dicumarol. *Ann. Int. Med.* 24: 648 (April) 1946.

Prothrombin activity was studied in the following subjects: nineteen patients with cardiac disease of heterogeneous types without embolism, thirteen patients with various types of cardiac disease and associated embolism, five noncardiac patients with thrombophlebitis and pulmonary embolism, and three noncardiac patients with thrombophlebitis without embolism. The "controls" were thirty-five healthy hospital workers or patients with "various diseases" whose nutritional status and physical condition were good. In the patients studied, serial prothrombin estimations were made from one to six times a week, and most cases were followed for two weeks or more. None of the patients received salicylates, and vitamin K and dicumarol were not given except in a few cases specifically studied. The readings included whole plasma prothrombin time and the 12.5 per cent diluted plasma prothrombin time, as recommended by Shapiro and others. The purpose of the dilution was to render ineffective the naturally occurring anticoagulants of the blood. For this reason, the authors place greater stress on the diluted plasma prothrombin time in evaluating their data. In the normal controls, the figures obtained by these authors were 17.8 ± 2 seconds (whole plasma) and 45.2 ± 5 seconds (diluted plasma). Of the eight cardiac cases with pulmonary embolism and infarction, four showed no deviation from normal, three showed an insignificant deviation, and only one showed any abnormal shortening of dilute plasma prothrombin time. In the two cases with myocardial infarction with mural ventricular thrombosis and peripheral embolism, and in the three cases of chronic rheumatic heart disease with auricular thrombosis and associated embolism, increased prothrombin activity was not present. Of the five noncardiac patients with thrombophlebitis and pulmonary embolism, all showed normal whole plasma prothrombin times, but four showed accelerated diluted plasma prothrombin time. On the contrary, of the cases of thrombophlebitis without embolism, only one manifested a shortened diluted plasma prothrombin time. Of the 19 cardiac patients without frank embolism (which included five patients with acute coronary occlusion and five with angina pectoris) an abnormal acceleration of the diluted plasma prothrombin time was encountered only three times, but in two of these instances, pulmonary infarction could not be entirely excluded. It is significant that digitalization, bed rest, or congestive failure did not significantly modify the prothrombin times. Six cardiac patients were given dicumarol therapeutically after embolism appeared. In all these, a significant prolongation of prothrombin time was achieved with less than the usually recommended amounts. The authors, therefore, suggest a tentative dosage schedule for cardiac patients. It is their opinion that the ideal indication for the use of this drug in cardiac disease is the presence of phlebothrombosis or thrombophlebitis. They also caution that dicumarol should never be used unless there are facilities for accurate daily estimations of prothrombin. Included in the paper is a lengthy and complete discussion of the technical considerations involved in the performance of tests for prothrombin time.

WENDKOS.

Charr, R., and Swenson, P. G.: Clubbed Fingers. *Am. J. Roentgenol.* 55: 325 (March) 1946.

The superficial arterial vessels were studied by these authors in six early cases of clubbed fingers to further aid in understanding the pathogenesis of this condition. No bone changes were demonstrable by the roentgenogram. Injections of diodrast into the radial arteries in several patients were first tried but were technically unsatisfactory. The

methods finally used were infrared photography in the living, and injection of a suspension of barium sulfate post mortem. Three of these patients had died of advanced pulmonary tuberculosis. The clinical findings in the remaining three living patients were advanced bronchiectasis, pulmonary necrosis following pneumonia, and pulmonary tuberculosis associated with congenital stenosis of the pulmonary artery. None of the six cases had evidence of congestive heart failure. They found an increase in the number of blood vessels, with wider lumina, about the tips of the fingers.

The authors state that while their observations substantiated the anatomic studies previously described, the results of their study of blood flow in patients with clubbed fingers were at some variance with the reports of others. The prevailing opinion seems to be that the bone changes, the hypertrophy, and the hyperplasia of the soft tissues present in clubbing result largely from the increased nutrition brought about by increased peripheral blood flow.

MERANZE.

Parker, R. L., Dry, T. J., Willius, F. A., and Gage, R. P.: Life Expectancy in Angina Pectoris. *J. A. M. A.* 131: 95 (May 11) 1946.

Recent follow-up studies of patients with angina pectoris have shown a favorable lengthening of the average survival period. These authors made follow-up studies on 3,440 cases of angina pectoris. The average age of the patient at the time of onset was 57.1 years. The majority of the patients had suffered with angina pectoris for a period of two years or less prior to the examination (74.3 per cent). In 2.8 per cent, symptoms of angina pectoris had been present for ten years or more prior to the time of examination. The ratio of men to women was 4.3:1. The highest mortality date was observed in the first year following examination. During this year, 18 per cent of the patients succumbed. Following the first year, the mortality remained nearly constant, averaging approximately 10 per cent among those who had survived the disease for three years. The survival rate was higher for women than for men. Associated conditions, such as cardiac hypertrophy, well-defined hypertension, previous cardiac infarction, congestive heart failure, and significant electrocardiographic abnormalities were clearly related to a higher mortality rate and lower survival rate.

BELLETT.

Gregg, D. E.: The Coronary Circulation. *Physiol. Rev.* 26: 28 (Jan.) 1946.

This article consists of a review of the coronary circulation particularly from the standpoint of physiology and pharmacology. There is a brief résumé of the anatomy and the experimental approaches to the study of the coronary circulation. The various methods of measuring coronary blood flow are discussed and some points of possible error and inadequacy of these measurements as applied to the problem in man are emphasized. The author brings out the fact that the reported observations dealing with the coronary flow, its minute volume, distribution, and ultimate drainage, its response to drugs, the effects of nervous and humoral influences, and the effects of changes in aortic pressure, peripheral resistance, cardiac output, cardiac work, and metabolism are often made upon preparations that are abnormal and under conditions that are artificial. All too often results obtained with a decidedly abnormal preparation ultimately come to be regarded as events which can and do occur in the normal animal or man. Various concepts concerning the coronary circulation have frequently been revised, as new and improved instruments and preparations have been developed. Much of what has been reported in the past should be discarded as more accurate methods for making the same physiologic studies become available. He concludes that until better instruments and methods are devised and used in conjunction with preparations which are capable of normal physiologic responses, our knowledge concerning the normal and abnormal functioning of the coronary circulation will be necessarily limited as well as unavoidably inexact.

BELLETT.

Norpoth, L., and Vagades, K.: Disturbances of the Pacemaker and of Conduction in Addison's Disease. *Ztschr. f. Kreislaufforsch.* 35: 673 (Dec.) 1943.

The literature reporting electrocardiographic findings in Addison's disease is reviewed. Among the abnormalities reported have been varying degrees of A-V heart block, prolongation of the Q-T interval, low voltage, T-wave inversion, and, sometimes, RS-T segment depression. One case is added by the authors. The patient was a 31-year-old man, with a minor grade of A-V heart block in which the P-R interval shortened to top-normal duration with exercise. During a subsequent crisis sinus arrhythmia, bradycardia, extrasystoles, and periods of sinoauricular heart block or A-V nodal rhythm appeared. All of these abnormalities disappeared following the administration of cortical hormone. SAYEN.

von Diringshofen, H., Sarie, H., and Strnad, W.: Study of the Roentgen Density of the Lungs in Humans as a Measure of the Pulmonary Blood Flow. *Ztschr. f. Kreislaufforsch.* 35: 462 (Aug.) 1943.

The authors believe that variations in the roentgen density of the peripheral lung field in excess of those occurring with normal respiration should provide an index of the pulmonary blood content. Their method was to measure the illumination of a portion of the right lung by a photoelectric cell in front of a fluoroscopic screen. By the use of a tilt table, the variation in lung density of normal subjects in various positions could be studied. The roentgen density of the lung decreased significantly with shifts from the erect to the recumbent position. The head-down position increased the density, and light exercise had a similar effect. Changes in the degree of density under these conditions were several times greater than those resulting from quiet respiration. When the breath was held against a pressure of about one atmosphere, decrease in density was observed; a further decrease in density was observed to follow shifts from the vertical to the horizontal position. Administration of low-oxygen mixtures and of adrenalin or histamine produced no significant effects. The authors concluded that, contrary to expectations, the blood content of the lungs decreases in recumbency in spite of increased venous return. The mechanism is obscure. The possibility of arteriovenous anastomotic channels opening to permit a more rapid pulmonary blood flow in the horizontal position is suggested. SAYEN.

Holmgren, B. S.: The Movements of the Mitro-Aortic Ring Recorded Simultaneously by Cineroentgenography and Electrocardiography. *Acta radiol.* 27: 171 (No. 2) 1946.

The movements of a sharply outlined calcific deposit in the mitral valve ring were studied in two patients by making cineroentgenograms at 16 frames per second and simultaneously recording an electrocardiogram with a signal marking the time of the successive exposures. It was found that the calcific shadow moved apically just after the beginning of the QRS complex and continued to do so until the end of the T wave. During the latter part of the isoelectric period the shadow moved slowly back toward the base, stopped briefly at the beginning of the P wave, and then moved a little farther basally until just after the beginning of the next ventricular complex. The total distance traveled was about 2 cm.: a considerably greater distance than the amplitude of the ventricular wall pulsation. Thus, the mitral ring appeared to move upward toward the base with auricular systole and downward toward the apex with ventricular systole, which was in accord with other observations in the literature. SAYEN.

Bernstein, G.: Treatment of Acute Arrhythmias During Anesthesia by Intravenous Procaine. *Anesthesiology* 7: 113 (March) 1946.

Previous experimental data have shown that the intravenous or intracardiac injection of procaine into anesthetized dogs which had developed serious cardiac arrhythmias

resulted in recovery and restoration of normal rhythm. It is emphasized that the intravenous injection of procaine or other local anesthetic agents is to be scrupulously avoided in the conscious patient, in whom it may produce cardiovascular collapse or stimulation of the central nervous system to the point of generalized convulsions. However, the tolerance to procaine in the anesthetized subject is different from that of unanesthetized individuals. In experimental work on dogs anesthetized with cyclopropane, 150 mg. of procaine was injected intravenously without any evidence of untoward effects.

In the series of patients reported by the author, the single dose of procaine used in the anesthetized patient ranged from 30 to 70 milligrams. No deleterious effects were observed; on the contrary, cardiocirculatory improvement was often effected. The author related his experience with single-dose injections intravenously into fourteen anesthetized patients with acute arrhythmias during intrathoracic operations. The arrhythmias always improved dramatically.

The use of procaine during anesthesia to diminish cardiac irritability was based upon a number of findings. Investigators have shown that procaine applied locally to the heart reduced the irritability of the myocardium. It has also been established that during chloroform anesthesia the injection of procaine protects against the development of ventricular fibrillation produced by epinephrine. Cardiac arrhythmias produced by epinephrine during cyclopropane anesthesia in dogs can be abolished by procaine after such arrhythmias have been established. Previous studies have also shown that when the ventricular fibrillation sets in during cyclopropane anesthesia, the intracardiac injection of procaine is usually followed by a return of sinus rhythm.

In discussing the efficacy of the use of procaine, it is stated that general anesthesia probably affords specific protection against the stimulating action of procaine on the central nervous system. Further studies are needed, however, to determine the optimal dose.

BELLETT.

Noble, R. P., Gregersen, M. I., Porter, P. M., and Buckman, A.: Blood Volume in Clinical Shock. II. The Extent and Cause of Blood Volume Reduction in Traumatic Hemorrhagic and Burn Shock. *J. Clin. Investigation* 25: 172 (May) 1946.

The mechanism of traumatic shock is similar to that of hemorrhagic shock in that the plasma proteins and the erythrocytes alike are lost from the circulating blood in proportional amounts, and hemodilution occurs to compensate for the reduction in circulating blood volume. The inference is that severe skeletal trauma is accompanied by loss of whole blood into the injured tissues and that a generalized increase in capillary permeability does not occur in these conditions. On the contrary, burn shock and peritonitis are accompanied by hemoconcentration due to loss of plasma at the site of injury.

FRIEDLAND.

Weens, H. S., and Heyman, A.: Cardiac Enlargement in Fever Therapy Induced by Intravenous Injection of Typhoid Vaccine. *Arch. Int. Med.* 77: 307 (March) 1946.

The effects of febrile illnesses upon the heart, particularly in the precipitation of heart failure, are discussed by the authors. During the treatment of patients with neurosyphilis with fever induced by intravenous administration of typhoid vaccine, these authors observed roentgenographic evidence of cardiac enlargement in a significant number of cases. Cardiac enlargement was present in eight of fifteen patients during the period of fever therapy. Increases in the transverse diameter varying from 1 to 2.3 cm. were observed. In two patients there was associated pulmonary congestion.

The increase in the heart size was usually recognized by the end of the first week, but was more pronounced after the second or third week of therapy. Regression of the increased heart size usually occurred during the month following fever.

BELLETT.

Cosgrove, E. F., and Caravati, C. M.: Salicylate Toxicity: The Probable Mechanism of Its Action. *Ann. Int. Med.* 24: 38 (April) 1946.

The recent vogue for massive salicylate therapy in rheumatic fever has introduced several problems, one of which is the troublesome nausea and vomiting which develops during treatment. The purpose of this study was to determine whether such symptoms are due to the action of the drug upon the gastrointestinal mucosa or to a central stimulation of the vomiting center. To test the validity of each view, data were compiled from gastroscopic examinations, estimations of the salicylate level in the blood, determination of the concentration of salicylic acid in the gastric aspirates, and analyses of salicylate in the urine before and after administration of alkalis. According to the authors, the results in a limited number of patients indicated that nausea was experienced more often by patients who received the drug intravenously than by those who received it orally, and that a definite correlation could be established between the nausea and a critical level of the salicylate concentration in the blood. It was observed also that the administration of alkalis relieved the nausea in the group receiving the drug intravenously as well as in those who received it by mouth. The factor presumed to be responsible for this relief was increased urinary excretion of salicylate which followed the administration of the alkali. Finally, it was observed that salicylic acid was absent in the gastric aspirates of patients in whom the blood level of salicylate was high, and by gastric examination no gastric lesions could be seen in those receiving massive doses of salicylate, either orally or intravenously. The authors conclude that the gastrointestinal symptoms which appear during massive salicylate therapy are due to the action of the drug on the cerebral nerve centers and not to any local effect on the alimentary tract.

WENDKOS.

Whitehorn, W. V., Edelmann, A., and Hitchcock, F. A.: The Cardiovascular Responses to the Breathing of 100 Per Cent Oxygen at Normal Barometric Pressure. *Am. J. Physiol.* 146: 61 (April) 1946.

Following a fifteen-minute rest period, normal subjects breathed 100 per cent oxygen for sixty minutes. The cardiac output was determined by the ballistocardiographic method. A significant reduction in cardiac output, amounting to -0.63 to -0.98 liters per minute, was observed; the percentage change was -13 per cent to -19.4 per cent. Subjects breathing room air for a sixty-minute period displayed smaller changes in cardiac output amounting to -0.06 to 0.22 liters per minute; the percentage change was -1.3 to -4.9 per cent. These latter figures were considered to have no statistical value. The reduction in cardiac output was effected by means of a decline both in the heart rate and in stroke volume. Systolic arterial pressure did not change significantly; however, at the end of the sixty-minute test period, diastolic pressure averaged 7 mm. Hg higher than the control value.

FRIEDLAND.

DeLaBarreda, P.: The Significance of Cardiac Weight in Rats With Experimental Hypertension. *Rev. clín. españ.* 19: 167 (Nov. 15) 1945.

Hypertension was produced in rats by the use of Goldblatt's clamp and the production of cellophane perinephritis. After hypertension had become established, the cardiac and total body weights were correlated in accordance with Addis' formula. Normal animals were used as controls. Although cardiac hypertrophy usually develops with persistent experimental hypertension, the author found that hypertrophy does not always occur. Moreover, hypertrophy was sometimes found in normal rats without hypertension. Hence, the determination of cardiac weights is not an adequate criterion of the past status of the arterial hypertension.

GOLD.

Repetto, R., Ferrari, J. A., and Benzecri, I.: Rupture of Aortic Valves Due to Effort. *Prensa méd. argent.* 44: 2171 (Nov. 2) 1945.

A case of rupture of the leaflets of the aortic valve following sudden severe effort is reported. The authors distinguish between rupture due to effort and that caused by trauma to the chest. In the former the lesion occurs at the angle of attachment of the leaflets to the aortic wall while in the latter the rent occurs at the free valvular margins. The characteristic murmur is heard at some distance from the heart in rupture due to effort, while in trauma to the chest it is usually confined to the precordium. The rupture is due to sudden increase in the intra-aortic pressure and the inability of the valves to withstand the augmented diastolic recoil of the column of blood. Antecedent disease such as atherosclerosis or syphilis increases the vulnerability of the valves. The increase in the aortic pressure is the result of increased cardiac output following increased venous return which occurs during the deep breathing that precedes sustained effort, the fixation of the chest and the squeezing of the subclavian and carotid vessels by the contracted muscles of the neck, shoulders, and arms, and the outpouring of adrenalin during effort.

The characteristic sign and symptom is the murmur of which the patient as well as his neighbors may become acutely aware, and which is best described as the "cooing of a dove."

Finally, the authors call attention to a symptom-free period lasting from minutes to weeks that may occur between the causative effort or trauma and the appearance of the characteristic murmur. Its recognition is important from the legal standpoint, since total disability follows rupture of the aortic valves. Left ventricular enlargement and failure occur sooner or later in the course of the disease, and subacute bacterial endocarditis may be a complication. In the early period, both the electrocardiogram and the x-ray studies of the heart are negative.

GOLD.

Stryker, W. A.: Coronary Occlusive Disease in Infants and Children. *Am. J. Dis. Child.* 71: 280 (March) 1946.

Considerable interest has been aroused recently in the incidence of coronary occlusive disease in young soldiers. The importance and nature of coronary occlusive disease in a still younger age group, namely, that of infants and children, has not been fully appreciated. In adults, the great majority of coronary occlusions are related to arteriosclerotic disease of the atheromatous type. In infants and children, however, that type of arteriosclerosis is a relatively rare factor in causing occlusion and the incidence of other types is increased. The arterial lesions which may produce partial or complete occlusion in infants and children include medial calcification with fibroplastic proliferation of the intima, polyarteritis (periarteritis nodosa), syphilitic arteritis, embolism, congenital abnormalities, rheumatic arteritis, and hypertension. Stryker reports the findings in a series of hearts from nine infants and children under the age of 17 years, in whom occlusion of one or more coronary arteries is the important feature. He discusses each of the above categories and illustrates them with sections of the coronary arteries showing the different types of pathology producing coronary occlusion.

BELLET.

Wintrobe, M. M.: The Cardiovascular System in Anemia, With a Note on the Particular Abnormality of Sick Cell Anemia. *J. Hemat.* 1: 121 (March) 1946.

The author reviews the cardiovascular and physiologic adjustments which occur in the presence of anemia. These include increase in the cardiac rate, velocity of blood flow, minute volume, cardiac output, cardiac size, oxygen utilization and oxygen consumption; and decrease in the circulation time, the blood viscosity, the arterial blood pressure, the total blood volume, the A-V oxygen difference, and the vital capacity of the lungs. He suggests that the remarkable changes found in the cardiovascular system in cases of sickle cell anemia may be the result of adjustment to severe anemia of exceptional chronicity.

BELLET.

Pereiras, E., and Castellanos, A.: A New Indirect Radiologic Sign in the Diagnosis of Aortic Coarctation by Means of the Superior Retrograde Aortography. *Rev. cubana de cardiología* 99: 120, 1945.

This procedure of retrograde aortography is based upon the existence of anastomosis between the lateral thoracic, the superior intercostal and the internal mammary arteries arising from the aorta. Marked dilatation and tortuosity of these vessels are considered as pathognomonic of coarctation of the aorta. The notching along the inferior border of the rib is shown to be produced by the looping of the dilated intercostal vessels.

The authors' technique is as follows: a tight tourniquet is applied to the left arm distal to the site of injection. Twenty cubic centimeters of 50 per cent diodrast or neoipax is then injected into the left brachial artery at the antecubital fossa. Considerable resistance is usually encountered in overcoming the arterial blood pressure. No incision of the skin is necessary as a Lindemann catheter is used.

Usually the subclavian artery and part of the aorta are visualized; occasionally the abdominal aorta is seen. This technique was first tried in newborn infants but has since been used successfully in older children and adults without ill effect. TAVERAS

Firestone, G. M.: Meningococcus Endocarditis. *Am. J. M. Sc.* 211: 556 (May) 1946.

Although meningococcal infections are susceptible to the newer therapeutic agents, the fulminating character of the infection when it affects the valves of the heart, combined with the difficulties involved in establishing an early bacteriologic diagnosis, often conspire to delay therapy until the patient's condition is beyond the point of reversibility. The author describes in detail the clinical features of one case of meningococcal endocarditis, together with an analysis of twenty-four cases collected from the literature. He believes that the clinical picture is quite characteristic of this bacteriologically specific type of acute endocarditis; so much so that one may often obtain, in individual cases, a definite clue as to the etiological diagnosis. Most characteristic are the presence of skin lesions, arthralgia, and a tertian, quartan, or double quotidian type of temperature curve, together with the symptoms and signs of acute septicemia and physical signs of cardiac valvular involvement. DURANT.

Shanno, R. L.: Rutin: A New Drug for the Treatment of Increased Capillary Fragility. *Am. J. M. Sc.* 211: 539 (May) 1946.

Rutin, which is probably the active substance in citrin, is a crystalline glucoside of quercetin and a derivative of flavone. It is without either acute or chronic toxic effects when administered to animals. The author has experimented in human beings with this substance in doses of 20 mg. (occasionally higher) three times a day to determine its effectiveness in controlling increased capillary fragility as determined by the Göthlin test. No toxic effects were observed. Of thirteen hypertensive patients with increased capillary fragility all improved when treated with rutin. Eleven additional hypertensive patients received thiocyanate plus rutin. Seven of this group had normal fragility which was maintained by the prophylactic use of rutin with thiocyanate. Two patients treated solely with thiocyanate developed an increase in the Göthlin index, which became normal following treatment with rutin. One maintained a normal index on thiocyanate after an abnormal index had previously been created by rutin. Two cases of pulmonary hemorrhage of undetermined origin with increased capillary fragility were treated with rutin which restored a normal index and ended the bleeding. In three cases of increased capillary fragility, uncertain results were obtained due to drug reactions. One case of small hemorrhage into the eighth nerve nucleus and one with complete heart block and retinal hemorrhages returned to normal with rutin therapy.

It is concluded that rutin appears to be of value in: preventing vascular accidents in patients with hypertension, maintaining normal capillary fragility, avoiding vascular accidents in patients being treated with thiocyanate, and controlling pulmonary bleeding of undetermined origin. DURANT.

Book Reviews

INFECCAO REUMATICA E. CARDITE REUMATICA. By Moacir Carlos Barroso, Capitaó Medico do Exército. Grafica Laemmert Limitada, Rio de Janeiro, Brazil, 1945, 182 pages, 71 illustrations.

This monograph includes the personal experience of the author with rheumatic fever and rheumatic heart disease in a military hospital in Uruguayana in the Southern Brazilian state of Rio Grande do Sul. It also quotes the experience of Pedro da Cunha and his associates in Rio de Janeiro. A well-written and documented account is given of rheumatic fever and rheumatic heart disease. So far as we are aware, it is the most extensive review of the subject in Portuguese. Thus, the monograph is of considerable importance.

Of interest is the attention given by the author to the fact that, in the temperate zone areas of Brazil, there is a high incidence of rheumatic fever. This incidence is considered similar to that of other countries of like climates. In Brazil, the clinician has long been taught to think first of syphilis. A well-timed plea is presented for the clinician to remember that rheumatic fever is common and should not be neglected. The monograph deserves a wide circulation, and it will doubtless serve a most useful purpose.

PAUL SCHLESINGER, M.D., AND T. DUCKETT JONES, M.D.

CORNELL CONFERENCES ON THERAPY. Edited by Harry Gold, David P. Barr, McKeen Cattell, Eugene F. DuBois, and Charles H. Wheeler. New York, 1946, The Macmillan Company, vol. I, 322 pages.

In this book are contained what might be called teaching conferences given at Cornell to the undergraduates in medicine. Many will be familiar with this type of presentation as a number of these conferences have already appeared in the *Journal of The American Medical Association* and the *New York State Journal of Medicine*.

Designed to bridge the gap between the teaching of Pharmacology and of Therapeutics, members of the former department combine with doctors from the clinical departments to make the presentations, which are made in the form of a brief lecture followed by questions and answers. Drug therapy is discussed chiefly, but other forms of therapy, such as bed rest, are also covered. Apparently, further volumes are planned; the subject matter of this volume cannot be classified under one head.

The book can be highly recommended as a statement of modern therapeutic ideas.

ISAAC STARR.

American Heart Association, Inc.

1790 BROADWAY AT 58TH STREET, NEW YORK, N. Y.

DR. ROY W. SCOTT
President

DR. HOWARD F. WEST
Vice-President

DR. GEORGE R. HERRMANN
Treasurer

DR. HOWARD B. SPRAGUE
Secretary

BOARD OF DIRECTORS

*DR. EDGAR V. ALLEN Rochester, Minn.
DR. ARLE R. BARNES Rochester, Minn.
DR. WILLIAM H. BUNN Youngstown, Ohio
DR. CLARENCE de la CHAPELLE New York City
DR. NORMAN E. FREEMAN Philadelphia
*DR. TINSLEY R. HARRISON Dallas
DR. GEORGE R. HERRMANN Galveston
DR. T. DUCKETT JONES Boston
DR. LOUIS N. KATZ Chicago
*DR. SAMUEL A. LEVINE Boston
DR. GILBERT MARQUARDT Chicago
*DR. H. M. MARVIN New Haven
*DR. EDWIN P. MAYNARD, JR. Brooklyn
*DR. THOMAS M. McMILLAN Philadelphia
DR. JONATHAN MEAKINS Montreal
DR. E. STERLING NICHOL Miami

DR. HAROLD E. B. PARDEE New York City
DR. WILLIAM B. PORTER Richmond, Va.
DR. DAVID D. RUTSTEIN New York City
*DR. JOHN J. SAMPSON San Francisco
*DR. ROY W. SCOTT Cleveland
DR. FRED M. SMITH Iowa City
DR. HOWARD B. SPRAGUE Boston
DR. GEORGE F. STRONG Vancouver, B.C., Can.
DR. WILLIAM D. STROUD Philadelphia
DR. HOMER F. SWIFT New York City
DR. WILLIAM P. THOMPSON Los Angeles
DR. HARRY E. UNGERLEIDER New York City
*DR. HOWARD F. WEST Los Angeles
DR. PAUL D. WHITE Boston
DR. FRANK N. WILSON Ann Arbor
*DR. IRVING S. WRIGHT New York City
DR. WALLACE M. YATER Washington, D. C.

*EXECUTIVE COMMITTEE

DR. H. M. MARVIN, *Acting Executive Secretary*

ANNA S. WRIGHT, *Office Secretary*

TELEPHONE, CIRCLE 5-8000

THE American Heart Association is the only national organization devoted to educational work relating to diseases of the heart. Its activities are under the control and guidance of a Board of Directors composed of thirty-three eminent physicians who represent every portion of the country.

A central office is maintained for the coordination and distribution of important information. From it there issues a steady stream of books, pamphlets, charts, films, lantern slides, and similar educational material concerned with the recognition, prevention, or treatment of diseases of the heart, which are now the leading cause of death in the United States. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning the circulation of blood and lymph. Any physician or investigator may become a member of the section after election to the American Heart Association and payment of dues to that organization.

The income from membership and donations provides the sole financial support of the Association. Lack of adequate funds seriously hampers more intensive educational activity and the support of important investigative work.

Annual membership is \$5.00. Journal membership at \$11.00 includes a year's subscription to the AMERICAN HEART JOURNAL (January-December) and annual membership in the Association. The Journal alone is \$10.00 per year.

The Association earnestly solicits your support and suggestions for its work. Membership application blanks will be sent on request. Donations will be gratefully received and promptly acknowledged.

American Heart Journal

VOL. 32

SEPTEMBER, 1946

No. 3

Original Communications

ON EINTHOVEN'S TRIANGLE, THE THEORY OF UNIPOLAR ELECTROCARDIOGRAPHIC LEADS, AND THE INTERPRETATION OF THE PRECORDIAL ELECTROCARDIOGRAM

FRANK N. WILSON, M.D., FRANKLIN D. JOHNSTON, M.D., FRANCIS F. ROSENBAUM, M.D., AND PAUL S. BARKER, M.D., ANN ARBOR, MICH.

EINTHOVEN'S TRIANGLE

IN 1913, Einthoven, Fahr, and de Waart¹ published a method of estimating the direction and manifest magnitude, at a given instant in the cardiac cycle, of that component of the heart's electromotive force which is parallel to the plane defined by the standard limb leads. They utilized this method to study and to explain the modifications of the electrocardiographic deflections of these leads produced by respiratory variations in the position of the heart. The chief purpose which they had in mind seems to have been to find a way of distinguishing electrocardiographic phenomena due to extrinsic causes of this sort from those originating within the heart itself. More than thirty years have passed since this fundamental paper by Einthoven and his associates was written. No other has had so great an effect upon the development of our knowledge of the electrocardiogram; none has been the source of more inspiration; and none has been the subject of so much misunderstanding, so much critical examination, and so much controversial discussion. Why after all these years should there still be a wide difference of opinion regarding the correctness of the views expressed in this paper?

Unlike Einthoven and Fahr, the vast majority of those who have been engaged in the study of the human electrocardiogram have had small acquaintance

From the Department of Internal Medicine, University of Michigan Medical School.

This paper was presented in October, 1944, at a symposium held at Charity Hospital, New Orleans, under the auspices of the Medical School of Louisiana State University.

Many of the observations on which this paper is based were carried out with the help of a grant from the Horace H. Rackham School of Graduate Studies.

Received for publication Feb. 18, 1946.

with, and little interest in, mathematical attacks upon physical problems of the sort encountered in attempts to apply the classical theory of electricity to the analysis of the varying electrical field associated with the heartbeat. In theoretical investigations of this kind the actual situation under consideration is always far more complicated than any of those that can be treated mathematically, and it is necessary to make many simplifying assumptions that are not strictly in accord with the facts. To assert that all deductions based on such assumptions are *ipso facto* worthless is, so to speak, to deny that mathematics has contributed anything worth while to the physical sciences. To maintain, on the other hand, that deductions of this kind represent anything more than a first approximation to the truth or have any great value except in so far as they are supported by experience and by experiments designed to test their validity would be equally unreasonable. It is imperative that those who make use of conclusions of this sort as a guide to further investigations, or who attempt to extend them, clearly understand and constantly bear in mind the postulates upon which they rest.

Most of the controversies to which Einthoven's work has given rise seem to have originated in differences between the participants in respect to their familiarity with and their attitude toward its theoretical background. In our opinion, there is no reason to suppose either that Einthoven and his associates had any false notions as to the general character of the heart's electrical field or that they considered their method of determining the position of the electrical axis of the heart entirely free of error. In 1921, a paper by Lewis, Drury, and Iliescu² on the electrical axis of the auricle in clinical cases of auricular flutter raised a question as to the conditions under which the principles of Einthoven's triangle are applicable. A letter to Einthoven concerning this matter was answered by him on Nov. 21, 1921, as follows:

"In regard to the equilateral triangle I fully agree with you. I assumed in my original paper 'Ueber die Richtung und die Manifeste Grösse der Potentialschwankungen etc.,' in the center of the triangle a 'bipole,' that is to say two points lying very close together and showing a potential difference. The triangle was supposed to be a homogeneous sheet of conducting material and in regard to the distance between the two points of the bipole, of a large, let us say infinite extent.

"The applicability of this scheme to the ordinary leads of the human body depends indeed on the fact that the electrodes are at a relatively great distance from the heart. If they are placed near the heart the errors are greater and the more so the closer they get to the heart. Even in the case of the ordinary leads from the limbs the results cannot be absolutely exact."

A number of attempts have been made to test the validity of Einthoven's triangle by impressing a constant or variable voltage upon two metallic electrodes thrust into the heart of a cadaver and comparing the position of the electrical axis, computed by Einthoven's method from the potential differences recorded in the standard limb leads, with the direction of the impressed potential difference. The first experiment of this kind was performed by Fahr and Weber.³ The heart was exposed and two small zinc needles were thrust into its

wall, one in the region of the sinus node and the other at the apex. When 1/5 volt was applied to these electrodes the deflection in Lead I was 10 mm., that in Lead II was 46 mm., and that in Lead III was 36 millimeters. The angle between the line defined by the two electrodes and the direction defined by Lead I was estimated at 75 degrees. The corresponding angle computed from the deflections in the three leads was approximately 3 degrees larger.

A similar experiment was performed by Wagner⁴ on the cadaver of an infant who had died eight days after birth. In this instance two zinc needles were thrust through the precordial tissues into the heart and a potential difference of approximately 6 volts was impressed upon them. Three milliammeters were used to measure the resulting potential differences between the extremities. In the first test the currents in Leads I, II, and III were 6, 10, and 4 ma., respectively; when the input voltage was increased, these currents rose to 8, 13, and 5 ma., respectively. The chest was then opened, and it was found that one of the needles had entered the heart near its base, and the other entered just above the apex. The currents in the three leads were the same after opening the chest as before. When the electrodes were replaced so that the line defined by them made an angle of approximately 60 degrees with the direction of Lead I the currents in the three leads were 3, 6, and 3 ma., respectively. When the electrodes were arranged so that the line defined by them made an angle with the frontal plane, the currents in the standard leads were 3, 5, and 2 ma. when the projection of this line on the frontal plane was parallel to Lead II, and 4, 2, and -2 ma., respectively, when it was parallel to Lead I. This experiment and a large number of experiments on models of various types led Wagner to conclude (contra Groedel and Straub) that the theory of the equilateral triangle was in all respects well founded.

On March 1, 1934, Johnston, Kossmann, and Wilson⁵ performed an experiment on the cadaver of a man who had died of carcinoma of the face complicated by pneumonia more than a week before. During the interim, the cadaver had been stored in the morgue in the supine posture, and it was suspected that in addition to pronounced post-mortem changes there had been some gravitation of the body fluids into the more dorsal tissues. The input electrodes consisted of two small brass rods, insulated except at the sharpened tips and fixed in a wooden frame. The frame permitted the rods to be moved endwise so that when they were thrust into the precordium the depth of the tip of each rod was independently adjustable. By means of a rotating contact breaker a potential difference of approximately 18 volts was rhythmically impressed upon these electrodes after they were in place. The thickness of the chest, measured from precordium to back, was 21 centimeters. The electrodes were first thrust through the chest wall in the third intercostal space, one just to the right and the other just to the left of the sternum. The depth of the tip of the former (the negative electrode) was 5.7 cm. and that of the tip of the latter (the positive electrode) was 8.8 centimeters. The deflections recorded in Leads I, II, and III measured 26, 12.75, and -13 mm., respectively. Moving the left leg electrode to the pubis had no appreciable effect. Increasing the depth of the positive elec-

Norpoth, L., and Vagades, K.: Disturbances of the Pacemaker and of Conduction in Addison's Disease. *Ztschr. f. Kreislaufforsch.* 35: 673 (Dec.) 1943.

The literature reporting electrocardiographic findings in Addison's disease is reviewed. Among the abnormalities reported have been varying degrees of A-V heart block, prolongation of the Q-T interval, low voltage, T-wave inversion, and, sometimes, RS-T segment depression. One case is added by the authors. The patient was a 31-year-old man, with a minor grade of A-V heart block in which the P-R interval shortened to top-normal duration with exercise. During a subsequent crisis sinus arrhythmia, bradycardia, extrasystoles, and periods of sinoauricular heart block or A-V nodal rhythm appeared. All of these abnormalities disappeared following the administration of cortical hormone. SAYEN.

von Diringshofen, H., Sarie, H., and Strnad, W.: Study of the Roentgen Density of the Lungs in Humans as a Measure of the Pulmonary Blood Flow. *Ztschr. f. Kreislaufforsch.* 35: 462 (Aug.) 1943.

The authors believe that variations in the roentgen density of the peripheral lung field in excess of those occurring with normal respiration should provide an index of the pulmonary blood content. Their method was to measure the illumination of a portion of the right lung by a photoelectric cell in front of a fluoroscopic screen. By the use of a tilt table, the variation in lung density of normal subjects in various positions could be studied. The roentgen density of the lung decreased significantly with shifts from the erect to the recumbent position. The head-down position increased the density, and light exercise had a similar effect. Changes in the degree of density under these conditions were several times greater than those resulting from quiet respiration. When the breath was held against a pressure of about one atmosphere, decrease in density was observed; a further decrease in density was observed to follow shifts from the vertical to the horizontal position. Administration of low-oxygen mixtures and of adrenalin or histamine produced no significant effects. The authors concluded that, contrary to expectations, the blood content of the lungs decreases in recumbency in spite of increased venous return. The mechanism is obscure. The possibility of arteriovenous anastomotic channels opening to permit a more rapid pulmonary blood flow in the horizontal position is suggested. SAYEN.

Holmgren, B. S.: The Movements of the Mitro-Aortic Ring Recorded Simultaneously by Cineroentgenography and Electrocardiography. *Acta radiol.* 27: 171 (No. 2) 1946.

The movements of a sharply outlined calcific deposit in the mitral valve ring were studied in two patients by making cineroentgenograms at 16 frames per second and simultaneously recording an electrocardiogram with a signal marking the time of the successive exposures. It was found that the calcific shadow moved apically just after the beginning of the QRS complex and continued to do so until the end of the T wave. During the latter part of the isoelectric period the shadow moved slowly back toward the base, stopped briefly at the beginning of the P wave, and then moved a little farther basally until just after the beginning of the next ventricular complex. The total distance traveled was about 2 cm.: a considerably greater distance than the amplitude of the ventricular wall pulsation. Thus, the mitral ring appeared to move upward toward the base with auricular systole and downward toward the apex with ventricular systole, which was in accord with other observations in the literature. SAYEN.

Bernstein, G.: Treatment of Acute Arrhythmias During Anesthesia by Intravenous Procaine. *Anesthesiology* 7: 113 (March) 1946.

Previous experimental data have shown that the intravenous or intracardiac injection of procaine into anesthetized dogs which had developed serious cardiac arrhythmias

that of a dipole or doublet located in a homogeneous isotropic medium of large extent. In all probability this view was suggested by a well-known theorem on the potential of a complex of electric charges distributed in a dielectric and enclosed by a spherical surface of the smallest adequate radius. The potential of such a complex at any point outside this surface may be expressed in the form of an infinite series of spherical harmonics. When the net charge of the complex is zero, the successive terms of the series represent the potential of a dipole, the potential of a quadrupole, the potential of an octupole, and the potentials of multipoles of increasingly higher order.⁷ At points sufficiently distant from the center of the sphere the field may legitimately be regarded as closely approaching that defined by the first term alone, in other words, that of a dipole.⁷

Between the electrical field of a complex of charges of the kind described and the electrical field associated with the heartbeat, there is an obvious analogy. The sources and sinks of the heart's field corresponding to the positive and negative charges of the complex all lie within a circumscribed region: the smallest sphere in which the heart can be enclosed. The action current which flows out of any given cardiac fiber re-enters the same fiber in a neighboring region. Each source is, therefore, associated with a sink of equal strength, and it is clear that the cardiac field is not only comparable to that of a distribution in which the net charge is zero, but to a complex consisting of doublets only. Between an electrostatic field and the cardiac field there are, however, some obvious differences. In the first place, the latter, unlike the former, varies with the time. Nevertheless, the cardiac field at any given instant has always been treated as if it were stationary; the effects of induction have been neglected. The justification for this procedure lies in the low frequency of the cardiac currents, the relatively small size of the conductor involved, and the relatively small conductivity of the body tissues, and also in the results of experiments of the kind we have already described in which the distribution of variable currents of low frequency has been studied. In the second place, the heart is imbedded in a medium which is neither strictly homogeneous and isotropic nor infinite in extent. The effect of the requirements imposed by the boundary conditions involved is to superimpose upon the field of the cardiac sources and sinks, as it would exist in free space, the field of a layer of doublets at the body surface⁸ and the fields that would be produced by the presence of a single layer of charge on every surface separating tissues of unlike conductivity. The double layer is required to annul the field of the cardiac sources and sinks outside the body and each of the single layers to make the product of the conductivity and the electric intensity normal to the boundary surface the same on both sides of it. The effect of the double layer will, in general, be greatest at the body surface and least at points most distant from it; the effect of each single layer will be greatest near the surface on which it lies. It is, of course, out of the question to compute the exact effect of the boundary conditions that must be met in the case of conductors like the body which are irregular in shape and complicated as regards the arrangement and electrical properties of their constituent parts. It is possible, however, to compute the field of a centric or eccentric doublet in a sphere made up of spherical

trode to 10 cm. and decreasing the depth of the negative electrode to 5 cm. produced only very minor changes in the potentials of the three extremities, measured with respect to that of a central terminal connected to these electrodes and also to an electrode in the left interscapular region through resistances of 10,000 ohms. This procedure increased the positivity of the electrode on the back from 2 to 4.5 tenths millivolt.

When the positive electrode was in the third intercostal space near the left sternal edge with its tip 10.7 cm. below the skin, and the negative electrode in the fourth intercostal space and on the same vertical line but with its tip 5.5 cm. below the skin, the deflections in Leads I, II, and III measured 1.5, —30.5, and —32 mm., respectively. In this case, however, increasing the depth of the positive electrode to 15 cm. increased the deflection in Lead I to 12 and that in Lead III to —35 mm. and reduced the deflection in Lead II to —23 millimeters. The factor responsible for this unexpected result was not discovered.

These cadaver experiments by different workers support Einthoven's belief that when a potential difference is generated between two points lying within or close to the heart, the deflections in the three standard limb leads are very nearly proportional to the cosines of the angles made by the frontal projection of the axis of this potential difference with the corresponding sides of his equilateral triangle. It is, of course, true that the conductivity of dead tissues is by no means the same as the conductivity of living tissues. If experiments of the kind described could be performed on living subjects would the results be vastly different? In 1920, Wilson and Herrmann⁶ made a crude test of the validity of Einthoven's triangle in the course of some experiments on dogs in which the heart was stimulated rhythmically for the purpose of studying its refractory period. The stimulus was the current delivered by the secondary coil of an inductorium when the circuit through the primary coil was broken. Sharp deflections representing the induction shocks were observed in the limb leads. A stimulating electrode was then attached to each terminal of the secondary coil and the two electrodes were thrust into the ventral wall of the heart, one near the base and the other near the apex, in such a way that the line joining them was nearly parallel to the long axis of the body. The deflections produced by the induction shocks in the limb leads measured 2, 16, and 14 mm., respectively, under these circumstances. When the electrodes were so placed that the line joining them was perpendicular to the long axis of the body, these deflections measured 9, 3, and —6 mm., respectively. Except for the response to those shocks which fell outside the refractory period, the heart continued to beat normally. Its ventral surface was exposed and the lungs were not fully inflated. We doubt that the string galvanometer was capable of recording the very brief induction shocks with great accuracy. Nevertheless, it will be noted that the direction and relative size of the deflections in the limb leads were about what would be expected on the basis of the principles of the equilateral triangle.

It is clear that Einthoven regarded the electrical field associated with the heartbeat, in so far as it is represented by the potential differences recorded by the standard limb leads, as approximately equivalent at any given instant to

that of a dipole or doublet located in a homogeneous isotropic medium of large extent. In all probability this view was suggested by a well-known theorem on the potential of a complex of electric charges distributed in a dielectric and enclosed by a spherical surface of the smallest adequate radius. The potential of such a complex at any point outside this surface may be expressed in the form of an infinite series of spherical harmonics. When the net charge of the complex is zero, the successive terms of the series represent the potential of a dipole, the potential of a quadrupole, the potential of an octupole, and the potentials of multipoles of increasingly higher order.⁷ At points sufficiently distant from the center of the sphere the field may legitimately be regarded as closely approaching that defined by the first term alone, in other words, that of a dipole.⁷

Between the electrical field of a complex of charges of the kind described and the electrical field associated with the heartbeat, there is an obvious analogy. The sources and sinks of the heart's field corresponding to the positive and negative charges of the complex all lie within a circumscribed region: the smallest sphere in which the heart can be enclosed. The action current which flows out of any given cardiac fiber re-enters the same fiber in a neighboring region. Each source is, therefore, associated with a sink of equal strength, and it is clear that the cardiac field is not only comparable to that of a distribution in which the net charge is zero, but to a complex consisting of doublets only. Between an electrostatic field and the cardiac field there are, however, some obvious differences. In the first place, the latter, unlike the former, varies with the time. Nevertheless, the cardiac field at any given instant has always been treated as if it were stationary; the effects of induction have been neglected. The justification for this procedure lies in the low frequency of the cardiac currents, the relatively small size of the conductor involved, and the relatively small conductivity of the body tissues, and also in the results of experiments of the kind we have already described in which the distribution of variable currents of low frequency has been studied. In the second place, the heart is imbedded in a medium which is neither strictly homogeneous and isotropic nor infinite in extent. The effect of the requirements imposed by the boundary conditions involved is to superimpose upon the field of the cardiac sources and sinks, as it would exist in free space, the field of a layer of doublets at the body surface⁸ and the fields that would be produced by the presence of a single layer of charge on every surface separating tissues of unlike conductivity. The double layer is required to annul the field of the cardiac sources and sinks outside the body and each of the single layers to make the product of the conductivity and the electric intensity normal to the boundary surface the same on both sides of it. The effect of the double layer will, in general, be greatest at the body surface and least at points most distant from it; the effect of each single layer will be greatest near the surface on which it lies. It is, of course, out of the question to compute the exact effect of the boundary conditions that must be met in the case of conductors like the body which are irregular in shape and complicated as regards the arrangement and electrical properties of their constituent parts. It is possible, however, to compute the field of a centric or eccentric doublet in a sphere made up of spherical

shells of specified conductivities. On the basis of such computations, of the available experimental knowledge of the specific conductivities of the body tissues, and of the results of experiments of the kind described in previous paragraphs it seems to us that Einthoven's views as to the nature of the heart's electrical field, in so far as they are expressed in, or may be inferred from, his published work, are still in accord with all the known facts.

UNIPOLAR LEADS

In 1932, Wilson, Macleod, and Barker⁹ described a new type of electrocardiographic leads in which a central terminal connected through equal resistances to electrodes on the right arm, left arm, and left leg is paired with an exploring electrode placed on the precordium or upon any other part of the body. They held that leads of this kind are essentially unipolar in the sense that they record the potential variations of the exploring electrode with respect to a reference point which remains at very nearly the same potential throughout the cardiac cycle. It was shown that the sum of the differences in potential between any number of electrodes and a nodal point connected to these electrodes through equal resistances must be zero as a consequence of Kirchhoff's first law. The potential of the central terminal is consequently equal at every instant to the mean of the potentials of the electrodes on the extremities. On the basis of the assumptions upon which the equilateral triangle of Einthoven, Fahr, and de Waart is based plus the additional assumption that electrical forces of cardiac origin which are perpendicular to the plane of the standard limb leads have no significant effect upon the potential variations of the extremities, it was also shown that the potential of a central terminal connected through equal resistances to electrodes on the right arm, left arm, and left leg is not materially affected by the heartbeat and may be considered nearly constant throughout the cardiac cycle.

This conclusion promises to become the subject of a controversial discussion no different in character and not less lengthy than the one that has revolved around Einthoven's triangle. Several kinds of experiments bearing on its validity have been reported. Burger and Wuhrmann¹⁰ mention that one of them compared the potential of the central terminal of Einthoven's triangle with that of other central terminals each connected to three electrodes equidistant from the heart and lying at the apices of a triangle enclosing it. No details are given, but it is stated that the differences in potential between the various terminals were negligibly small. Arrighi¹¹ is known to have carried out experiments of a similar kind. So far as we know his work has not yet been published, but all of his experiments that we have knowledge of yielded results comparable to those reported by Burger and Wuhrmann. We have performed one experiment of the same kind and the results of such experiments are predictable on the basis of Arrighi's published work. In his doctoral thesis¹² he described his experience with three leads which formed the sides of a sagittal triangle that enclosed the heart. One electrode was placed in the left submaxillary region close to the chin, the second 3 or 4 cm. to the left of the midpoint of a line joining the umbilicus with the center of the pubis, and a third in the left interscapular space, approximately at

the level of the spinous process of the seventh thoracic vertebra. In almost all of the more than fifty cases of various types that were studied, it was found that the voltage of the deflection recorded at a given instant in the cardiac cycle by leading from the electrode on the jaw to that on the abdomen was very nearly equal to the sum of the simultaneous voltages recorded in Leads II and III divided by the square root of 3. It is not difficult to demonstrate algebraically that whenever this is the case the difference in potential between a central terminal connected to the usual extremity electrodes and a central terminal connected to Arrighi's submaxillary and abdominal electrodes only cannot be appreciably greater than that between his abdominal electrode and the left leg electrode. Since these two electrodes are similarly situated with reference to the heart we may expect that they will always be at nearly the same potential. A lead from the central terminal of Einthoven's triangle to a central terminal connected to all three of Arrighi's electrodes will, therefore, ordinarily yield deflections similar to, but approximately one-third as large as, those obtained by leading from the first of these terminals to the electrode on the back.

The tracings obtained in the only experiment of this kind that we have carried out are reproduced in Fig. 1. In addition to the standard and the unipolar limb leads (taken by Goldberger's method) the following special leads (taken with the electrocardiograph at twice the normal sensitivity) are shown: (1) a lead from the central terminal of the Einthoven triangle to a terminal connected to all three of the Arrighi electrodes; (2) the same lead after the electrode on the back had been disconnected from the second terminal; (3) the same lead after reconnecting the electrode on the back and disconnecting the electrode on the jaw; (4, 5, and 6) leads from the central terminal of the Einthoven triangle to each of the three Arrighi electrodes in turn; (7) a lead from the same terminal to one connected through equal resistances to two electrodes, one on the left back near the base of the neck and the other just to the left of the sacrum; (8 and 9) leads from the same terminal to each of these electrodes in turn. It will be noted that the greatest potential difference between the central terminal of the Einthoven triangle and that of the Arrighi triangle did not exceed 0.15 mv and that the first of these terminals was negative with respect to the other. It should also be noted that the deflections of Lead V_T , — V_T are similar to those of Lead V_B — V_T but about one-third as large.

In the case of normal subjects, an electrode placed on the back directly behind the heart is ordinarily positive with respect to the central terminal of the Einthoven triangle throughout the greater part of the QRS interval. For the time being we may assume, therefore, that this terminal is normally slightly negative and that of the Arrighi triangle slightly positive when the sagittal component of the heart's electromotive force has an anteroposterior direction. By connecting these two terminals together or by connecting an electrode on the back to the central terminal of Einthoven's triangle we might perhaps obtain a reference point more nearly indifferent than either.

Several investigators have attempted to ascertain the magnitude of the potential variations of the central terminal of Einthoven's triangle by means of

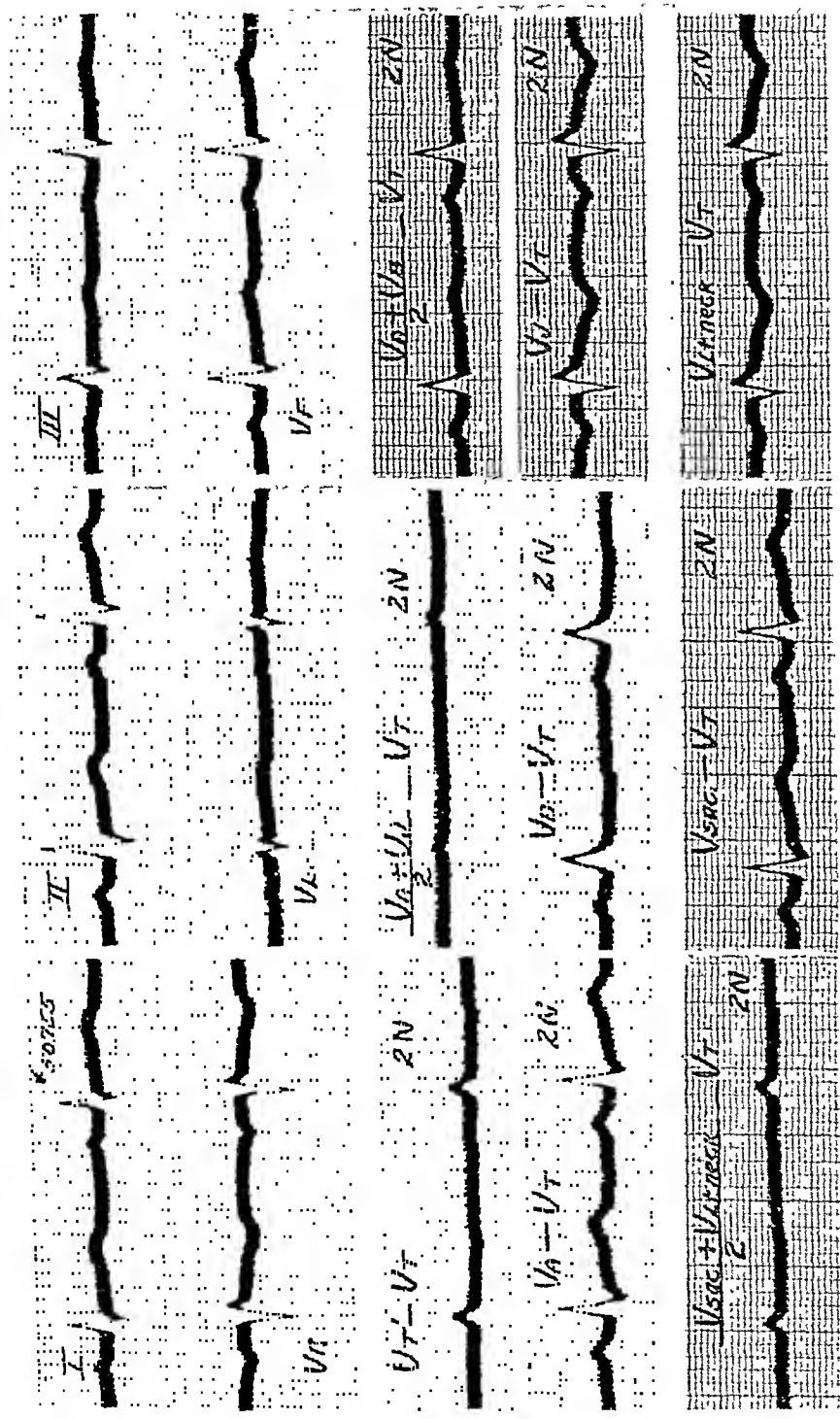


Fig. 1.—Comparison of the central terminal of the Einthoven triangle with that of the Arrighi triangle. A deflection of 2 cm. represents a voltage of 1 millivolt.

immersion experiments. Eckey and Fröhlich¹³ placed their subjects in a large wooden tub lined with metal and filled with distilled water; contact between the subject and the metal lining was prevented by a suitable wooden support. The surface of the water was screened by a sheet of metal placed beneath it and in contact with the metal lining of the tub. The subject breathed through a glass tube brought out through a small hole in this metal lid; other small openings accommodated the electrocardiographic cables. The electrodes employed were not insulated. It was found that immersion of the subject in distilled water did not materially reduce the size of the deflections in the standard limb leads and that the cardiac field did not extend to the water outside the metal screen. The largest potential variations of the central terminal with respect to this screen were of the order of 0.2 to 0.3 mv in all of the unspecified number of experiments performed.

Burger¹⁴ employed a tub lined with zinc and filled with tap water, and he did not immerse the face of his subjects. He insulated his electrodes from the bath with rubber sheeting. Immersion reduced the deflections of the standard limb leads to approximately 75 per cent of their original size. In five experiments on normal subjects the voltage of the largest deflection obtained by leading from the metal screen to the central terminal was about 0.26 millivolts. In four of the five cases the central terminal was slightly negative with respect to the zinc shield during the greater part of the QRS interval.

We have performed one immersion experiment of a somewhat different kind. After the standard limb leads had been taken, the subject was immersed up to the chin in a small fresh-water lake. The short-circuiting effect of the water reduced the size of the deflections in these leads to approximately one-half their original size (Fig. 2). There was also a slight change in the form of the ventricular complexes, probably because, when in the water, the subject was not able to assume exactly the posture in which the control curves were taken. The potential variations of the limb electrodes and the central terminal with respect to a large metal electrode suspended in the lake at a distance of about 11 feet from the body were recorded with an amplifier-type electrocardiograph at twice its normal sensitivity. The largest potential variation of the central terminal measured 0.15 mv; it was negative to the reference electrode (Fig. 3). The distant and the left leg electrode remained at practically the same potential throughout the cardiac cycle; we assume that in a series of experiments this would happen only rarely. Both arms and a point on the right scapula were negative with respect to the distant electrode during the greater part of the QRS interval.

Burger was uncertain as to whether the magnitude of the potential variations of the central terminal could be ascertained by the method which he employed for this purpose. Wolferth and Livezey¹⁵ have expressed the opinion that "the reason advanced by Eckey and Fröhlich to support the claim that their immersion procedure can be used to obtain unipolar leads has no merit." The lack of agreement exemplified by this comment is basically similar in origin to the controversy between the proponents of the "negativity hypothesis" and the proponents of the "doublet hypothesis" which began some ten years ago. As the

years have passed it has become more and more apparent that the chief sources of this controversy are differences in point of view, in opinion as to the proper choice of a reference point for the measurement of bio-electric fields, and in the sense in which the word "potential" is employed between those who are mainly interested in the action currents of isolated nerves bounded by a dielectric and those who are mainly concerned with the action currents of the heart which is imbedded in a conducting medium.* Because many who do not understand the nature of the dispute have become uncertain as to whether unipolar precordial and unipolar limb leads are desirable and as to whether they are theoretically or practically possible, we have re-examined and attempted to clarify the ideas upon which the concept of an indifferent electrode is founded.

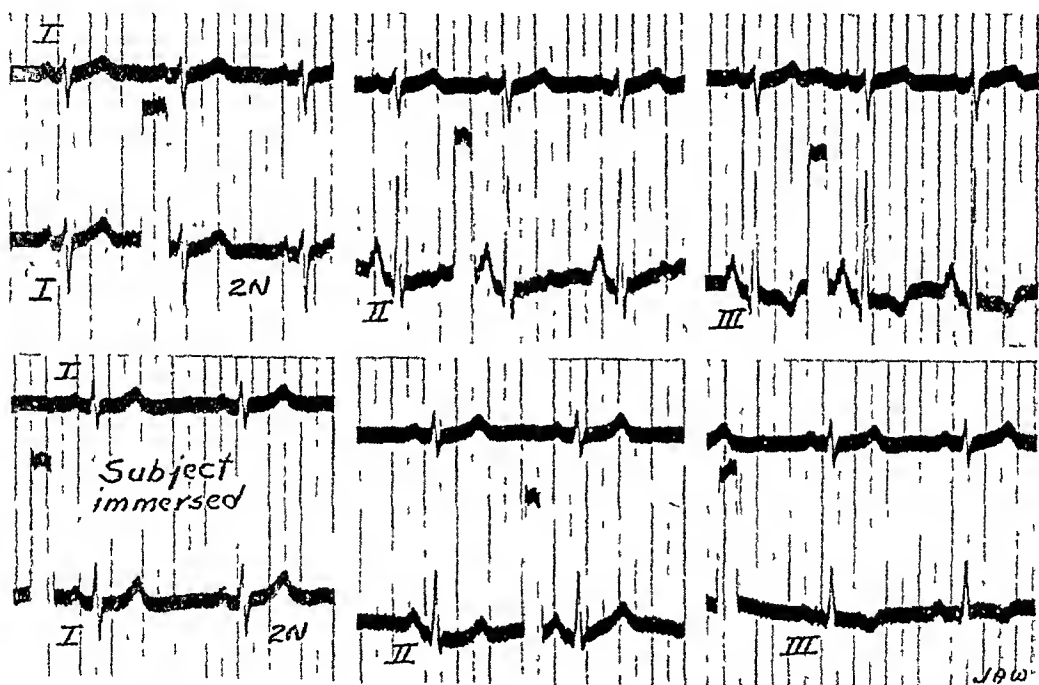


Fig. 2.—Electrocardiograms of a normal subject taken with the electrocardiograph at twice the normal sensitivity (2 cm. equals 1 mv).

The sequence of events and the considerations which led to the introduction of the central terminal for the purpose of obtaining unipolar leads are in outline quite simple. In 1916, Lewis and Rothschild¹⁷ had difficulty in recognizing the "intrinsic" deflection in leads in which paired contacts were placed on the exposed ventricular surface. They attributed this difficulty to the arrival of the impulse beneath both electrodes almost simultaneously. To avoid it they left one electrode in place and moved the other, sometimes to another part of the heart's surface, and sometimes to the chest wall. They found the last procedure par-

*The champions of the "negativity hypothesis" focus their attention upon the action potential, or time-course of the voltage across the cell membrane during excitation and therefore choose an injured region which is incapable of responding to the excitatory process as their reference point. (For a discussion of such leads see Col and Curtis¹⁶) Cardiologists who are forced to deal with the distribution of the cardiac action currents in a volume conductor are confronted by problems of an entirely different sort. They cannot apply the same principles to the interpretation of their tracings, must use the term "potential" in a different sense, and, consequently, must find another point of reference more useful for their purposes.

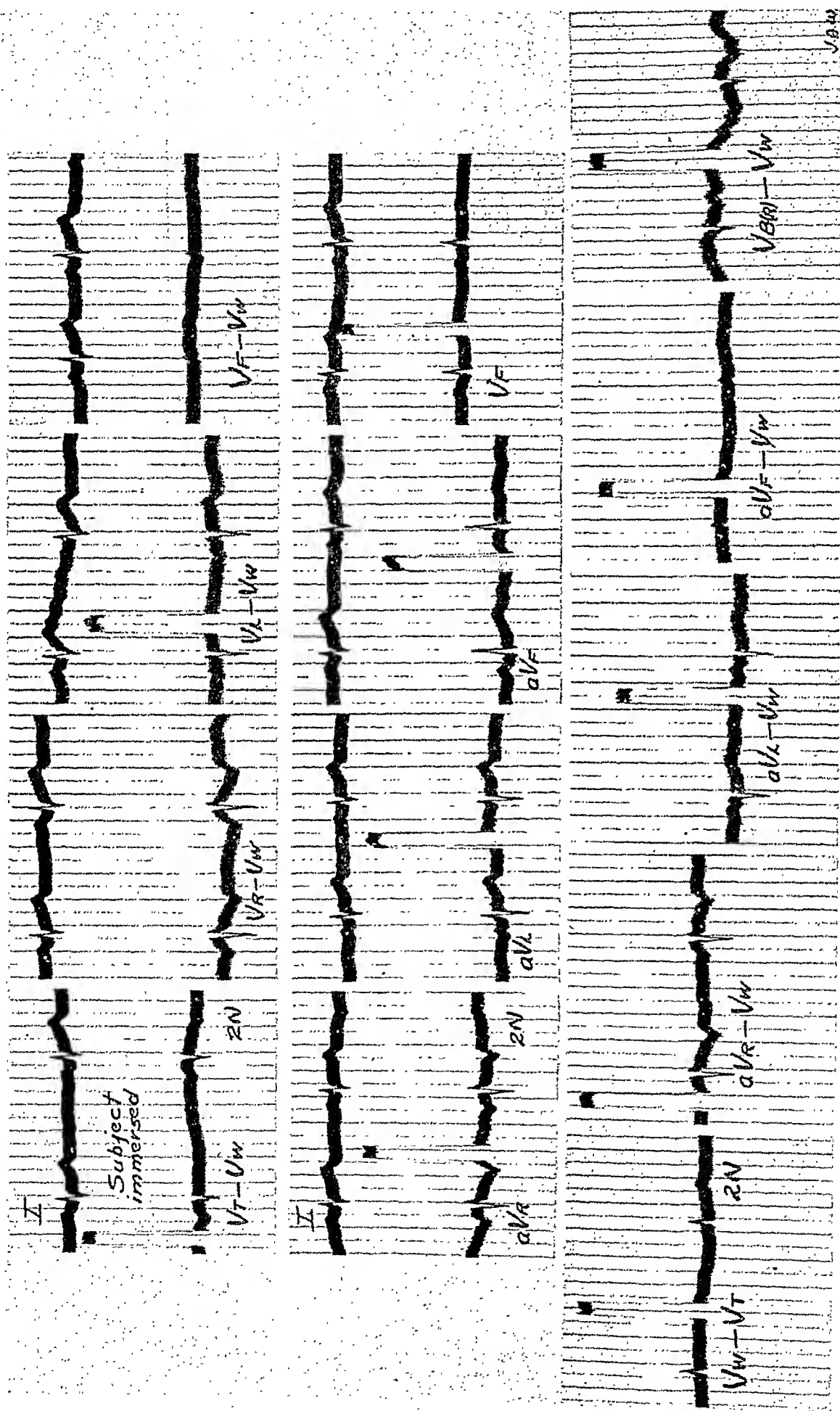


Fig. 3.—Records showing the potential variations of the central terminal and of electrodes on the extremities with reference to an electrode 11 feet from the subject. These tracings were taken with the electrocardiograph at twice the normal sensitivity. The symbols used have the following significance: V_R , V_L , and V_F represent the potentials of the electrodes on the right arm, left arm, and left leg, respectively, when connected to the central terminal through resistances of 5,000 ohms; aV_R , aV_L , and aV_F represent the potentials of these same electrodes when disconnected from the central terminal; V_F is the potential of the central terminal; V_w is the potential of the distant reference electrode; and $V_n(n)$ is the potential of an electrode on the right scapula. Leads from an extremity electrode to the central terminal are labelled V_n , etc., or aV_n , etc., in the usual way.

ticularly serviceable, and they clearly regarded the chest contact as without influence upon the position of the intrinsic deflection in the QRS interval. It is not certain that they considered this contact as indifferent in other respects; or that they believed the potential variations of this contact too small to have any significant influence upon the form of the tracings they obtained. In this laboratory the electrocardiograph is employed at one-twentieth of its normal sensitivity when leads of the kind in question are taken. So long as the distant contact is not placed close to the heart, its location can, therefore, have no important effect upon the size or form of the deflections recorded. On the other hand, moving the direct contact from one part of the heart's surface to another is almost certain to give the resulting curve an entirely different character. If we think of the cardiac field in terms of the current density, it is obvious that it is very intense in the vicinity of the epicardial surface, and, in comparison, of negligible strength in the neighborhood of the distant electrode. In the former region, the variations in the intensity of the field during the cardiac cycle are very large; in the latter they are very small. It is logical, therefore, when employing leads of this sort, to regard the potential variations recorded as characteristic of the region upon which the direct contact rests and to think of the distant electrode as indifferent and without influence upon the form of the curve; in other words, to consider leads of this kind unipolar.

In 1920, Wilson and Herrmann¹⁸ performed the following experiment. A line was drawn from the fourth left costal cartilage to a point on the left leg just below Poupart's ligament. A small electrode (A) was placed at the upper end of this line and similar electrodes (B, C, D, and E) were spaced along its course at points 5, 10, 15, and 20 inches, respectively, below the first. With the electrocardiograph at half the normal sensitivity, Leads A-B, B-C, C-D, and D-E were then taken. The largest QRS deflection measured 20 mm. in the first, about 3 mm. in the second, and about 1 mm. in the third of these leads. No deflection of any kind was visible in the fourth. The results of this experiment suggested that, if an electrode on the central part of the precordium were paired with a contact at a considerable distance from the heart, the form and size of the ventricular deflections obtained would be nearly the same regardless of whether the second electrode were above, below, to the right of, to the left of, or behind this organ. The experiment was tried and this conclusion was confirmed.¹⁹ Theoretical considerations and the resemblance in general contour between the ventricular complexes of leads in which a precordial electrode was paired with a contact far from the heart and those which Lewis and Rothschild obtained by leading from the epicardial surface of the exposed ventricles to some point on the chest wall led to the belief that leads of this kind are actually semidirect leads from the anterior ventricular surface, and this conclusion was published by Wilson, Wishart, and Herrmann²⁰ in 1926. A preliminary report of experimental and clinical observations bearing upon the value of such leads for the purpose of differentiating left from right bundle branch block was published in 1930 by Macleod, Wilson, and Barker.²¹ The publication of the complete account²² of these observations was postponed until the components of the human pre-

cordial curves which could legitimately be ascribed to potential variations of the distant electrode,²³ which had been placed on the left leg, could be computed and eliminated. The central terminal was introduced⁹ with the object of accomplishing the same purpose more directly by reducing the potential variations of the reference contact to a minimum. This seemed desirable in order to make precordial leads of the kind in question as nearly unipolar, and therefore as nearly comparable to direct leads of the sort used by Lewis and Rothschild, as might be possible.

The central terminal is founded upon the idea that, so far as the limb leads are concerned, the electrical field of the heart is approximately equivalent to that of a dipole lying in or near the plane of these leads and that the principles upon which Einthoven's equilateral triangle is based are sound. If this view is tenable the potential of this terminal should remain at nearly the same level throughout the cardiac cycle. It is true that the sum of the potentials at the apices of an equilateral triangle enclosing a centric dipole which varies in strength will not remain constant unless the plane which passes through the dipole and is perpendicular to its axis separates the conducting medium involved into two identical parts. It is also true that the body is not symmetric with respect to any plane that passes through the heart. On the other hand, the magnitude of the effects produced by a lack of symmetry with respect to any such plane must decrease as the distances from the heart to the boundaries responsible for it increase. It was shown, for example, by Wilson¹⁹ that when a coil of copper wire is placed in the field generated in a layer of electrolyte by a centric source and sink close together, the resulting modification of the field increases as the disturbing factor is brought closer to the region where the current density is maximal.

With respect to immersion experiments and the like, it is evident that factors which increase the asymmetry of the conducting medium surrounding the hypothetical cardiac dipole will tend to increase, and factors that have the opposite effect to decrease the potential variations of the central terminal with reference to a point that is completely indifferent. Placing the body in a lake or in a smaller body of water bounded by a metal screen, cannot change the location of the boundaries which define differences in tissue conductivity and it is hardly possible that it can significantly increase the flow of current across them. It does alter the heart's field by modifying the conditions at the body surface. The short-circuiting effect of the conducting fluid naturally reduces the potential differences between the various parts of this surface including those between one extremity and another and between the extremity electrodes and the central terminal. The magnitude of this effect is proportional to the conductivity of the water in which the body is immersed. The conductivity of distilled water is of the order of 2×10^{-4} mhos per meter and that of lake water and tap water is five to fifty times as great.⁷ If the potential variations of the three extremity electrodes are reduced proportionately and in the same measure as the differences in potential between them, the potential variations of the central terminal will be diminished in the same degree.

Even when it has comparatively little effect upon the size of the deflections in the limb leads, as in the experiments of Eckey and Fröhlich, or reduces the size of all these deflections in the same proportion, as in those of Burger, immersion of the body will not have the same effect upon the potential variations of all three extremity electrodes if it brings about differences in their spatial relations with respect to the new bounding surfaces. In experiments of the kind performed by the investigators just mentioned, a contact or near-contact between one of these electrodes and the shielding metal screen would bring both to the same or nearly the same potential. The difference in potential between the screen and the central terminal would then become equal or nearly equal to the difference in potential between the latter and the extremity electrode concerned. In other words, the effect of the asymmetric arrangement of the electrodes would be to make the potential variations of the central terminal with respect to the screen larger rather than smaller.

Whether bringing one of the extremity electrodes very close to the screen would alter the potential of the former, that of the latter, or that of both depends upon what is considered the proper reference point for the measurement of the potential of the cardiac field. By connecting the electrode or the screen to earth the absolute potential of either could be maintained at zero. Since the conductivity of metal is roughly fifty billion times that of distilled water, the intensity of the electric forces produced by the heart must be infinitesimal outside the metal shield, and we agree with Eckey and Fröhlich that the potential of the screen should be considered completely indifferent with respect to the cardiac field.

Differences of opinion on questions of this kind have led to much confusion. Their source lies in the circumstance that the absolute potential of a given point on an isolated conductor in which electric currents are flowing is indeterminate unless the total charge on the conductor is known or the potential of one of its points has been fixed by grounding it. This difficulty arises because an isolated conductor may carry a static charge of unknown magnitude. Such a charge over its surface will raise or lower the absolute potential by the same amount at every point of the conductor but will have no effect upon the currents flowing through it. In the case of an infinite conductor this situation cannot arise. If the conductivity of the isolated conductor under consideration is large enough, we may think of it as in contact over its whole surface with an infinite conducting medium possessing a very much smaller conductivity and thus make it possible, at least theoretically, to choose infinity as our reference point for the measurement of the field.

The electrical field associated with the heartbeat presents some additional complications because it varies with time. We have been treating it as though, at any given instant, it had the same characteristics that it would have if it were not changing. Let us suppose, therefore, that there is a static charge on the body (or any conductor of which it is a part) which varies in magnitude from instant to instant, and that the inductive effects of this varying charge may be neglected. The potential variations produced by it will then be of the same magnitude at every point of the conductor and will have no effect upon the cardiac currents.

Potential variations of this sort are imposed upon the cardiac field by selecting some arbitrary point on the body and grounding it, or what amounts in effect to the same thing, making it the reference point for the measurement of the potential. It is obvious that if the potential of any chosen point was not constant before, and is constant after it has been grounded, this procedure must either impose upon every other point of the conductor variations in potential of the same absolute magnitude as those abolished, or alter the distribution of the cardiac currents. Connecting the body to earth does not have an effect of the latter kind* large enough to be detected by the electrocardiograph.

If one investigator places his reference electrode on a freshly injured spot on the ventricular surface and connects it to earth, he will arrive at the conclusion that all ventricular complexes represent a combination of two monophasic responses. Another who places his reference electrode on an uninjured part of the ventricular surface will not find this view attractive. In leads from all parts of the body surface each will record large complexes that are practically identical in form, and both will disagree with a third investigator who has placed his reference electrode as far from the heart as possible and believes that the magnitude of the potential variations produced by the heartbeat diminishes rapidly as the distance from the heart increases. As to the variations in the difference in potential between two specified points on the body surface, all will come to the same conclusion only if they compare them directly by leading from one to the other, for neither of the first two investigators will be able to estimate these potential differences by comparing leads from each of the two points to his reference electrode unless he makes use of a measuring machine. It is clear that the arbitrary choice of a reference point for the measurement of the cardiac field in terms of the potential, and also a purely empirical approach to the selection of the most useful bipolar leads, is likely to yield a harvest of confusion rather than enlightenment. We can, of course, give up the concept of the potential and think of the field of the heart in its vector form; that is to say, as a distribution of electric currents. Unfortunately, vector fields, in which three numbers must be associated with every point, are much more difficult to visualize and to analyze than scalar fields.

Three-dimensional fields of any kind, vector or scalar, are difficult to visualize unless they have some degree of symmetry. In the case of a field that has this property, it is profitable to fix the attention upon the point, line, or plane with respect to which the symmetry subsists. There is nothing to be gained by choosing a reference point for the measurement of the potential in such a way as to give the measured cardiac field a less symmetrical aspect than that which it has when expressed as a system of current lines and isopotential surfaces. If this is to be avoided the potential of the reference electrode should be the same as that of the point or points with respect to which the cardiac field is most nearly symmetrical;

*It would seem that in this case the fluctuating charge on the body is represented by a flow of charge into and out of a condenser of which the plates are the body and the earth. Both the capacity of this condenser and the resistance in series with it are small, so that the time constant of the circuit involved must be very short, and the static charge involved very small. There is no chance that the redistribution of the amount of electricity required to change the potential of the body with reference to the earth by a few millivolts could be detected by any instrument used to take electrocardiograms.

better still, if it were possible, the same as that of points far enough from the heart to be beyond an appreciable influence of this field. In the latter case the potential would be zero where the intensity of the field was negligible. The potential of the central terminal is the mean of the potentials of the apices of Einthoven's triangle and these are nearly as far from the heart as any other points on the trunk. If the field of the heart, so far as its least intense parts are concerned, may be regarded as nearly equivalent to that of a dipole located within the heart, the potential of this terminal is also that of the center of the dipole, the point about which the cardiac field is most nearly symmetric, provided that the electric forces perpendicular to the plane of the limb leads have no significant effect upon the mean potential of the extremities.

If the potential variations of the reference electrode are large, the ventricular complexes of all leads from regions where the cardiac field is considerably weaker and therefore varies less will be very much alike in form. The occurrence of strikingly similar complexes in leads from points that are widely distributed over the body and differ greatly in respect to distance and direction from the heart is a clear indication that the reference electrode is far from indifferent. If the cardiac field at points far from the heart is nearly equivalent to that of a doublet, leads from two points equidistant from this organ and at opposite ends of a line which passes through its center should yield complexes exactly opposite in character if the leads employed are unipolar. The average potential over a spherical surface, due to charges within it, is zero if the net charge is zero²⁴ as in the case of dipoles. It seems probable, therefore, that the average of the *cardiac potential** over the body surface must have a small value. If the reference electrode is indifferent and complexes of one kind are obtained from all parts of a region close to the heart, such as the precordium, complexes of the opposite type should be obtained from a still larger diametrically opposite region, such as the back, which is farther away from the heart. So far as we are able to judge from our experience with the central terminal, its potential is ordinarily close to the average of that of the body surface.

In concluding this discussion we may emphasize the fact that all of the available data which have a bearing upon the questions at issue are consistent. This is a very important consideration in estimating their significance. The cadaver experiments indicate that in spite of the irregular shape of the body and the somewhat eccentric position of the heart it is possible to ascertain the orientation of the frontal projection of the heart's electrical axis with considerable accuracy by Einthoven's method. All the immersion experiments that have been carried out gave substantially the same results. In the case of normal subjects the potential of the central terminal with respect to an electrode which bore essentially the same relation to all or nearly all parts of the body surface was slightly negative throughout the greater part of the QRS interval and did not vary through a range of more than 0.3 millivolts. The chief question that arises in connection with these experiments concerns the relative magnitude of the potential variations of the central terminal before immersion with respect to its potential

*We use this term to indicate the potential of the cardiac sources and sinks under the boundary conditions imposed upon the field to which they give rise

variations after immersion. Due allowance has been made for the short-circuiting effect of the water on the basis previously indicated. That other factors, such as large variations in skin resistance from point to point, which might alter the magnitude of the potential variations in question when the subject was immersed could have had substantially the same effect in all the experiments performed seems very improbable. The observations on the difference in potential between the central terminal of the Einthoven triangle and that of the Arrighi triangle suggests that the small negative potential of the former observed in the immersion experiments was due to the effect of electric forces having an antero-posterior direction. It is desirable to know the magnitude of the error involved in determining the inclination of the sagittal projection of the heart's electrical axis by Arrighi's method. This organ is closer to the anterior wall of the chest than to any other part of the body surface and its position with respect to his triangle is not precisely the same as its position with respect to the triangle of Einthoven.

THE INTERPRETATION OF THE PRECORDIAL ELECTROCARDIOGRAM

A comprehensive article²⁵ on this subject has recently been published from this laboratory. We propose here to supplement and not to repeat what was said in that article. We shall confine our remarks to a few examples of types of precordial electrocardiograms that have not been adequately discussed.

Incomplete Right Bundle Branch Block.—The electrocardiogram reproduced in Fig. 4 is that of an obese boy, aged 9 years, who had a speech defect and displayed evidence of general hypoplasia and mental retardation. The heart was not enlarged, no significant murmurs were heard, and the blood pressure was 96/40. There was no history of cyanosis at birth and none was present at the time of the examination. The limb leads show rather pronounced left axis deviation, a QRS interval which measures approximately 0.09 second, and both an R and an R' wave in Lead III. Double R waves are also present in precordial leads V₁, V₂, and V_E. We believe that many precordial electrocardiograms of this kind represent incomplete right bundle branch block. We have encountered them frequently in all types of heart disease and also in many instances in which there was no other evidence of heart disease. Our interpretation of these curves is based on the occurrence of ventricular complexes of the same form in an electrocardiogram which was discussed in the article previously referred to (see Figs. 14 and 15 of that paper²⁵). In that instance they alternated with complexes characteristic of complete right branch block, and the initial phases of the two types of complexes were identical in all leads. The difficulty is that one often sees an embryonic secondary R, that is to say, a conspicuous notch on the ascending limb of S, or a small terminal R' deflection in Lead V₁ in cases in which there is not only no other evidence of heart disease but no increase in the QRS interval and no trace of a similar deflection in Lead V₂ or Lead V_E. The diagnosis of incomplete right bundle branch block must, therefore, be made with caution. We think that this diagnosis is more likely to be correct when the secondary R

wave is conspicuous and is present in Lead V_E as well as in Lead V_1 and the QRS interval measures at least 0.10 second in the limb leads. This diagnosis should not be made unless the R' deflection rapidly decreases in size as the exploring electrode is moved toward the left side of the precordium as it invariably does in complete right branch block. In some cases Lead V_1 displays an unusually prominent R deflection with a prominent notch or slur on its ascending limb, and if the exploring electrode is moved farther to the right a broad bifid R or a final R' deflection is recorded. This situation is illustrated in Fig. 5, in which is reproduced the electrocardiogram of a boy, aged 17 years, who had a very loud, rasping

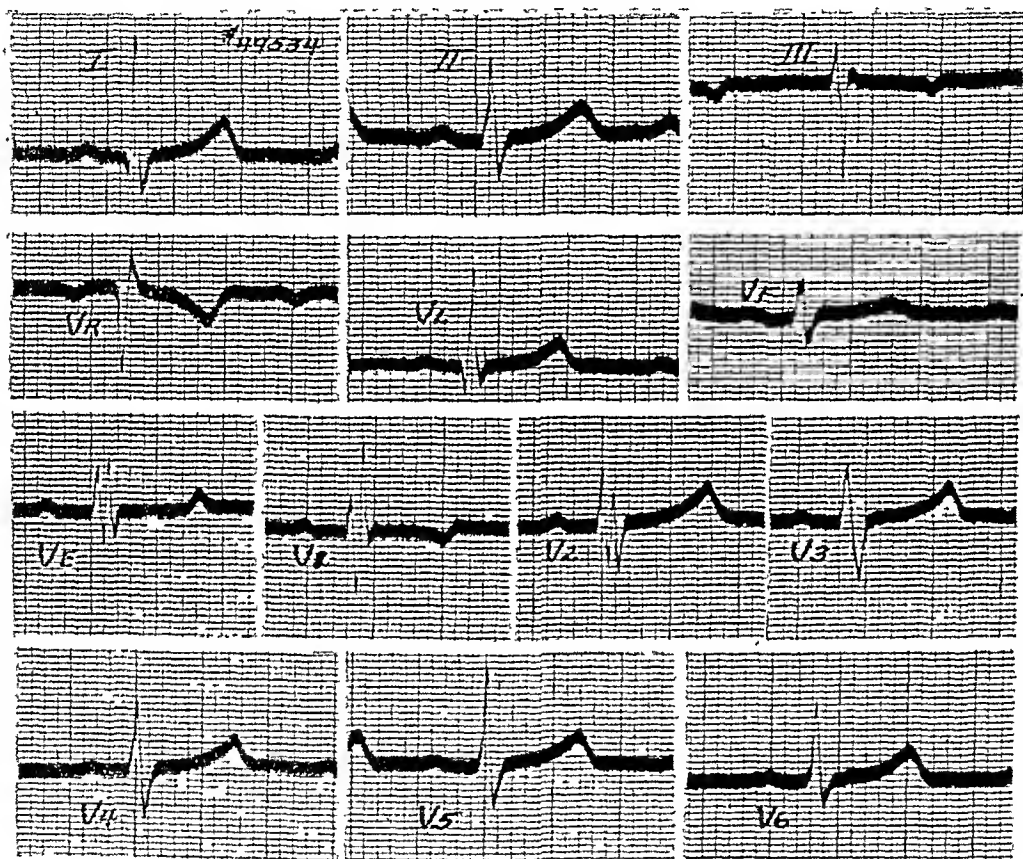


Fig. 4.—Incomplete right bundle branch block.

systolic murmur accompanied by a thrill in the pulmonic area. He was not blue at birth but a cardiac abnormality was noted a year later. There was no cyanosis and roentgenographic examination of the heart was negative. The position of the electrical axis, the small size of the R wave in Lead V_6 and in the leads from the left back (V_7 and V_8), and its large size in the leads from the right side of the precordium suggest right ventricular hypertrophy. However, this abnormality, which was suspected on clinical grounds also, does not satisfactorily explain the occurrence of secondary R waves in the leads from the right side of the chest.

Occasionally, we have seen precordial electrocardiograms which had all the characteristics of those that are diagnostic of complete right bundle branch block

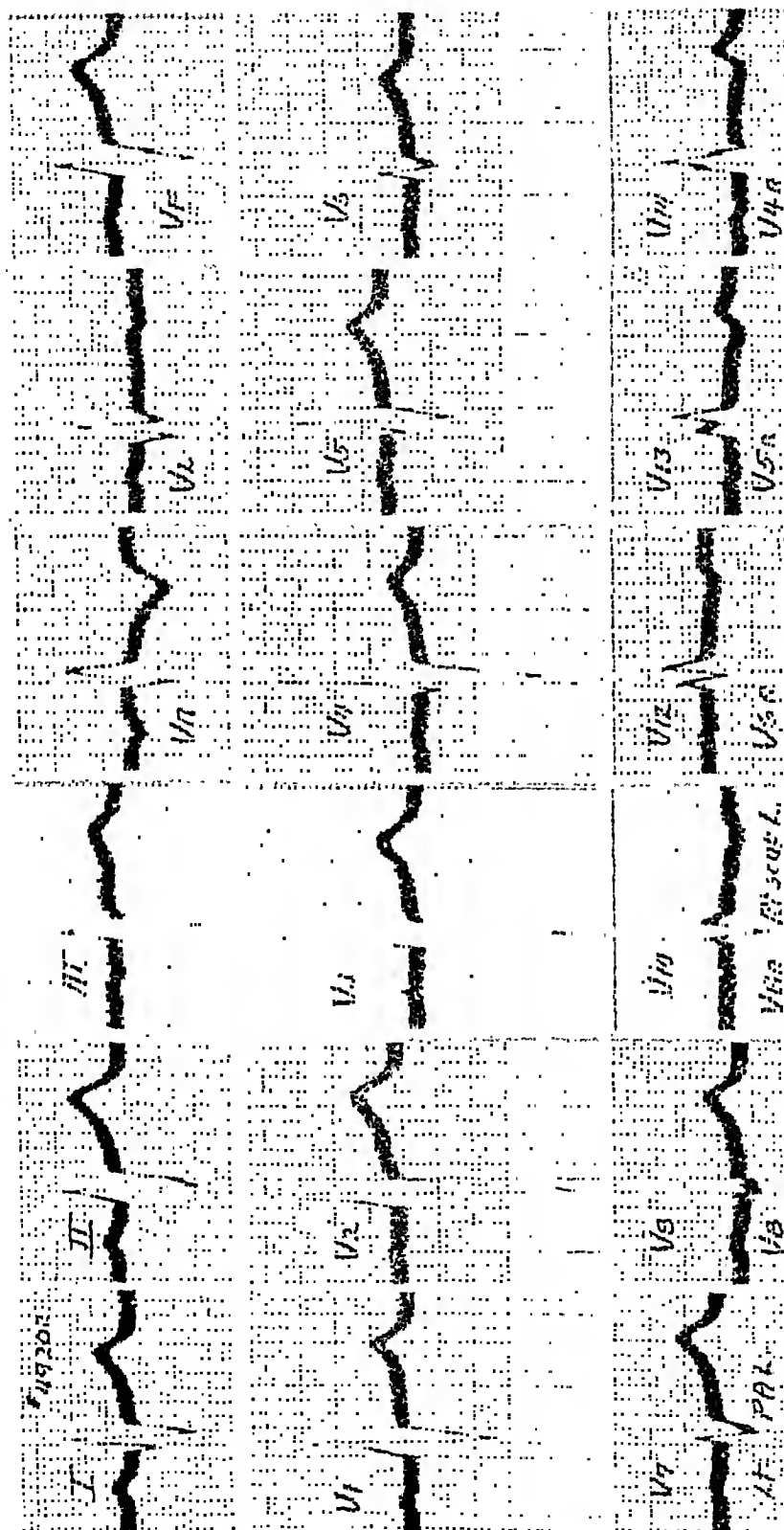


Fig. 5.—Somewhat questionable example of incomplete right branch block in a patient with a congenital heart lesion and right ventricular hypertrophy.

except that the QRS interval did not exceed 0.10 second. Most, if not all, of these have been obtained in cases in which there were clinical reasons for supposing that the right ventricle was carrying an abnormally heavy burden. We are inclined to believe that such tracings represent the combined effect of right ventricular hypertrophy and incomplete right branch block, possibly resulting from the high pressures sustained by this chamber.

Incomplete Left Bundle Branch Block.—This condition is still more difficult to diagnose with confidence than incomplete right branch block. It is probable that it often gives rise to electrocardiograms that are indistinguishable from those considered characteristic of left ventricular hypertrophy. This opinion is supported by an observation made by Dr. John B. Levan. He has been kind enough to send us for teaching purposes the electrocardiogram of a young man who was able to engage in strenuous exercise and appeared to be healthy in every respect. Ordinarily, his electrocardiogram was of the normal type but on one occasion it displayed, off and on, sequential complexes showing pronounced left axis deviation and deeply inverted T deflections in Lead I. The QRS interval of these complexes was slightly longer than that of the normal complexes, and the transitions from the abnormal to the normal mechanism were abrupt. It is evident that disturbances in intraventricular conduction that behave in this manner must involve only a single strand of specialized tissue, for it is hardly likely that several bundles would always cease to function and always recover at the same instant. Transient incomplete left branch block seems, therefore, to be the logical diagnosis in this case.

The electrocardiograms reproduced in Fig. 6 are those of a man, aged 49 years, whose blood pressure had been extremely high for a period of at least five years and who died of congestive cardiac failure in June, 1944. The first tracings, taken on May 23 of that year, are quite characteristic of complete left bundle branch block. The QRS interval measures approximately 0.17 second. On May 29, however, the QRS interval had decreased to between 0.09 and 0.10 second although the QRS deflections of the limb leads still showed conspicuous slurring and notching. The precordial curves of the same date are similar to those obtained in many cases of hypertensive heart disease. Note, however, that no Q wave is present in either Lead V_5 or V_6 . We have observed the same sequence of events in a number of other instances. The question arises as to whether the second set of curves represents incomplete left branch block, some other conduction defect, left ventricular hypertrophy alone, or a combination of the last two. If the first is the case, the earliest phases of the QRS complex of the same lead should have exactly the same outline in both sets of tracings. Unfortunately, this valuable criterion is often less useful than might be expected. The delay in the activation of the left ventricle may be nearly as great in incomplete as in complete left branch block or it may be very slight. If the latter is the case, the decision must be made on the basis of the form of the QRS complex during the first 0.01 or 0.02 second of the QRS interval; it will be noted, in the present instance, that in Leads V_1 , V_2 , V_3 , and V_4 the resemblance between the earliest phases of QRS in the two sets of curves is pronounced. In Leads V_5 and V_6 ,

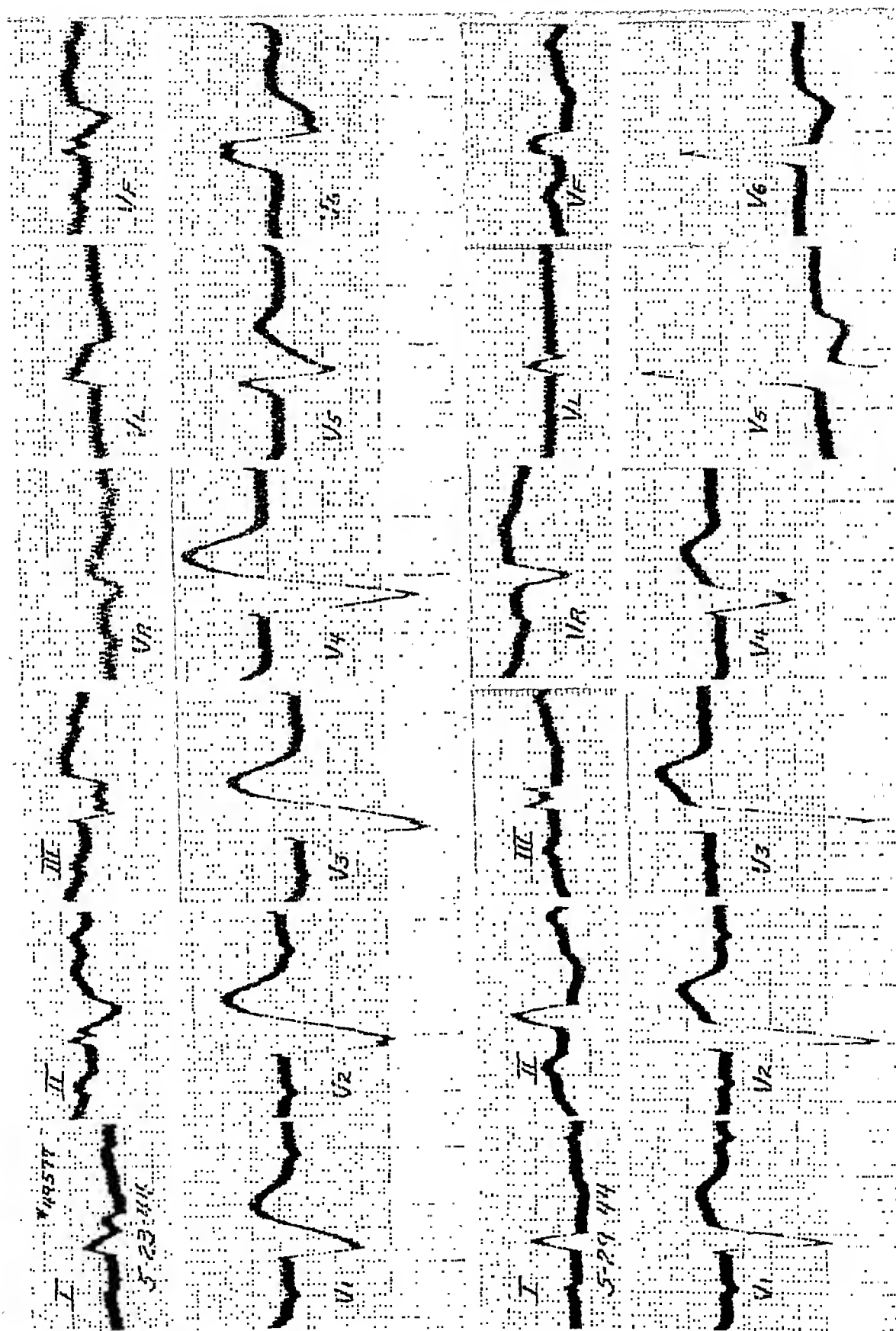


Fig. 6.—Transient complete left bundle branch block in a case of left ventricular hypertrophy possibly complicated by incomplete left bundle branch block.

the R wave begins with a slowly rising portion in the curves of the second set, but the slope of this initial component appears to be much steeper than the corresponding part of the R wave in those of the first set. About the only thing that can be said is that if the last set of tracings represents left ventricular hypertrophy plus incomplete left branch block, the delay in the activation of the left ventricle caused by the latter was slight. If a Q wave were present in the second set of leads from the left side of the precordium, the presence of this conduction defect could be ruled out with reasonable certainty.

In some cases in which incomplete left branch block is suspected, the precordial and extremity curves are like those of complete left branch block in every respect except that the QRS interval is less than 0.12 second.

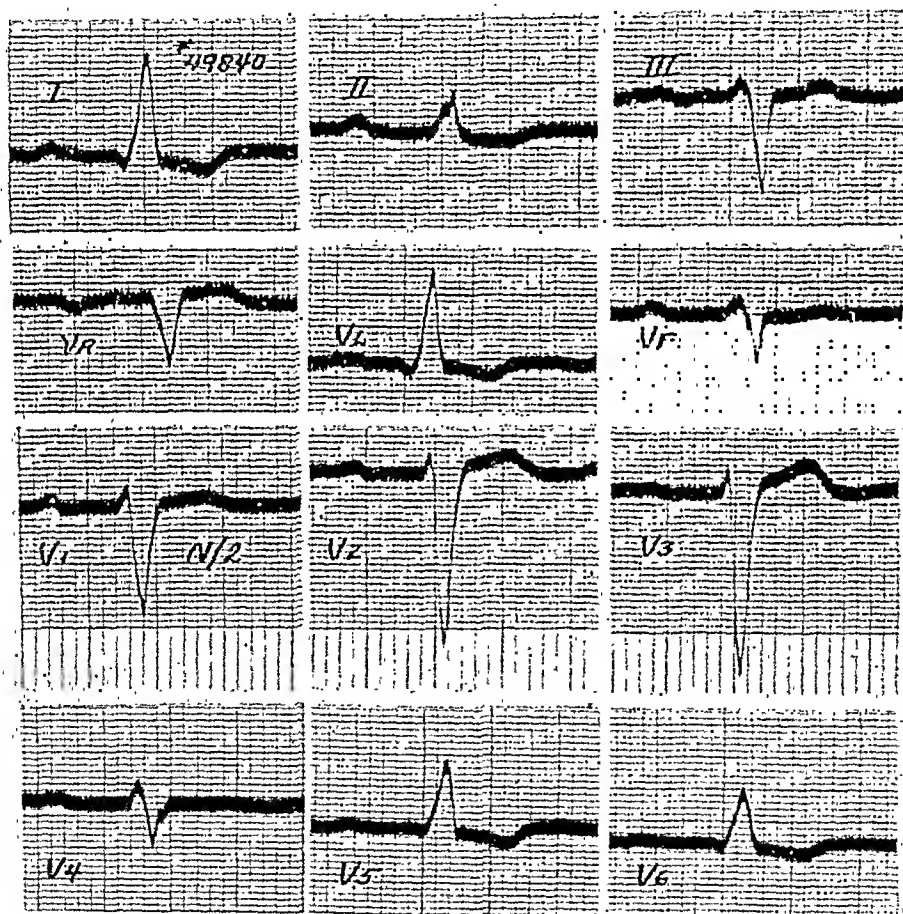


Fig. 7.—Left ventricular hypertrophy possibly complicated by a defect in intraventricular conduction.

Left Ventricular Hypertrophy.—A problem closely related to the one just discussed is presented by the electrocardiogram reproduced in Fig. 7, which is that of a man, aged 35 years, who had mitral stenosis, aortic regurgitation, and pronounced cardiac enlargement. The standard limb leads show conspicuous left axis deviation and inversion of the T wave in Leads I and II. The P-R interval is abnormally long and the QRS interval measures 0.12 second. Because

of the large voltage of the QRS deflections, the precordial leads were taken with the electrocardiograph at one-half its normal sensitivity. There is a conspicuous Q wave in Lead I and a small Q in Lead V₆. The R wave of the last of these leads is not broad-topped or bifid, as it usually is in complete left branch block, but there is some slurring and notching of the QRS deflections of the limb leads. The large voltages recorded in Leads V₁, V₂, and V₃ strongly support the diagnosis of left ventricular hypertrophy, but was this condition present alone, in combination with complete or incomplete left branch block, or in combination with some other conduction defect? In our opinion, the presence of a Q in Lead I and particularly in Lead V₆ plus the absence of a broad-topped or bifid R wave in the latter make the second possibility very unlikely. It is difficult to decide between the other two.

The electrocardiogram reproduced in Fig. 8 is that of a physician, aged 29 years, with mitral stenosis, aortic insufficiency, and pronounced cardiac enlargement. The limb leads show slight right axis deviation and changes in the P waves of the type commonly associated with an advanced mitral lesion. The P-R interval is slightly prolonged and the QRS interval measures approximately 0.105 second. The QRS deflections are slurred. The precordial curves are much more like those seen in left ventricular hypertrophy than like those associated with extreme right ventricular hypertrophy. The voltages of the deflections are not, however, extremely large and the T waves are normal. This electrocardiogram represents either auricular hypertrophy plus left ventricular hypertrophy, or plus hypertrophy of both ventricles. An increase in the QRS interval is rarely encountered in the electrocardiograms which are typical of preponderant right ventricular hypertrophy.

Pulmonary Embolism.—The electrocardiograms shown in Fig. 9 are those of a woman, aged 39 years, who was subjected to a subtotal hysterectomy plus appendectomy on May 26, 1944. On June 6 it was noted that Homans' sign was present, and on the following day at 8 p. m. the patient had a severe attack of chest pain accompanied by faintness and dyspnea. The blood pressure fell to 70/50. The first electrocardiogram was taken at 9:40 p. m. on June 8 and the second was taken at 4:45 p. m. on June 9. The patient died about five hours later and the post-mortem examination showed massive pulmonary embolism, pulmonary arteriosclerosis with organizing and recanalized thrombi, and some active pulmonary arteritis. The heart was not grossly abnormal. The two sets of limb leads are very similar; both show prominent S waves in Lead I and rather conspicuous Q waves in Lead III. The T waves are pointed in Leads II and III and there is a sharp bend in the initial limb of the T complex in Leads I and III. The QRS interval is a little longer in the second set of curves.

The two sets of precordial curves are very different. The first set is notable chiefly for the slight downward RS-T displacement in Leads V₃, V₄, and V₅ and for the sharp angulation of the ascending limb of T in these leads. The second set shows late R waves in Leads V_E and V₁ and sharply inverted T waves in the same leads and is strongly suggestive of incomplete right bundle branch block. It is well known that transient complete right branch block often occurs

in pulmonary embolism and that it is frequently followed by incomplete right branch block of gradually decreasing grade. In many cases, a conduction defect of this sort may account for all of the electrocardiographic abnormalities present. In the present instance, however, there were changes of the kind that have been considered characteristic of pulmonary embolism at a time when the precordial leads showed no evidence of a defect in conduction of the kind in question.

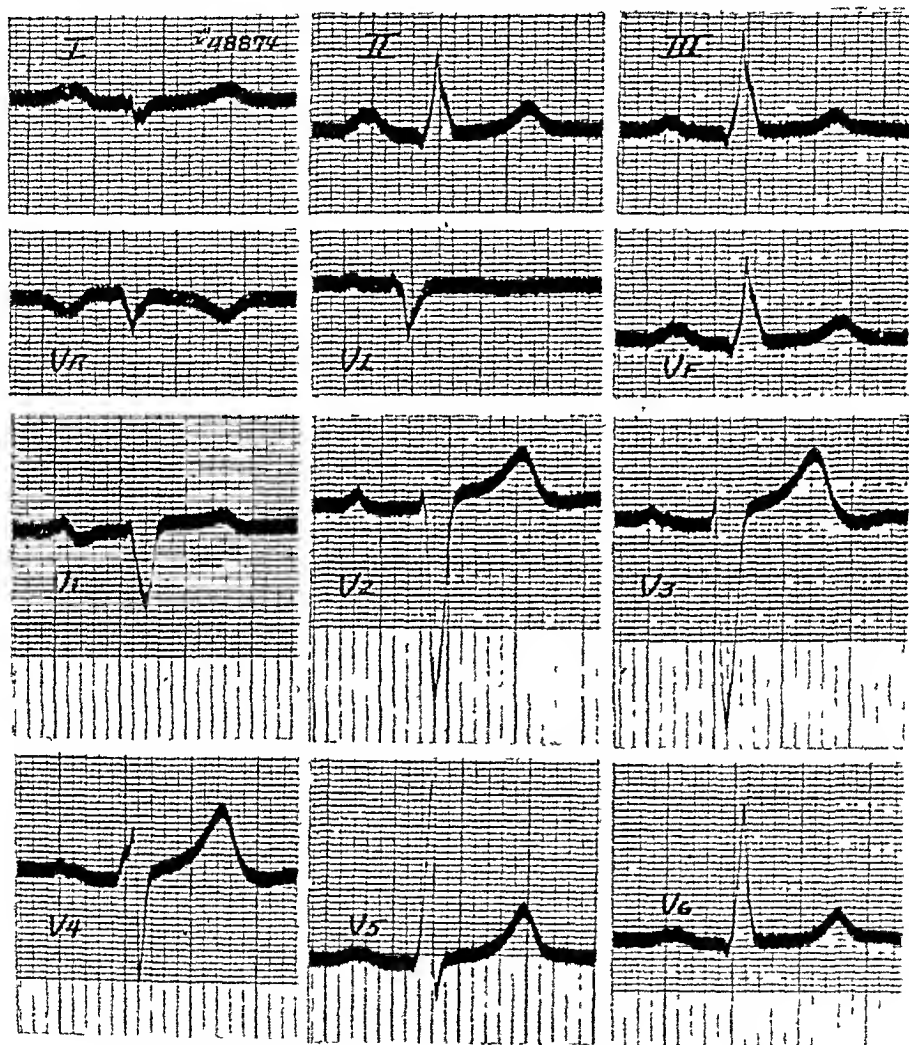


Fig. 8—Left ventricular hypertrophy or hypertrophy of both ventricles.

Anterior Infarction.—When the anterior wall of the left ventricle is infarcted the resulting changes in the QRS and T complexes are seldom more pronounced in Lead I than in precordial lead V₅. If the anteroseptal wall of the left ventricle is involved, the diagnostic electrocardiographic signs are usually confined to one or more of the first four precordial leads and the complexes of the limb leads are either of the normal type or show modifications of the T waves only. If the anterolateral wall is involved, diagnostic changes are present in Lead I and Lead V_L and in some combination of the precordial leads which includes Lead

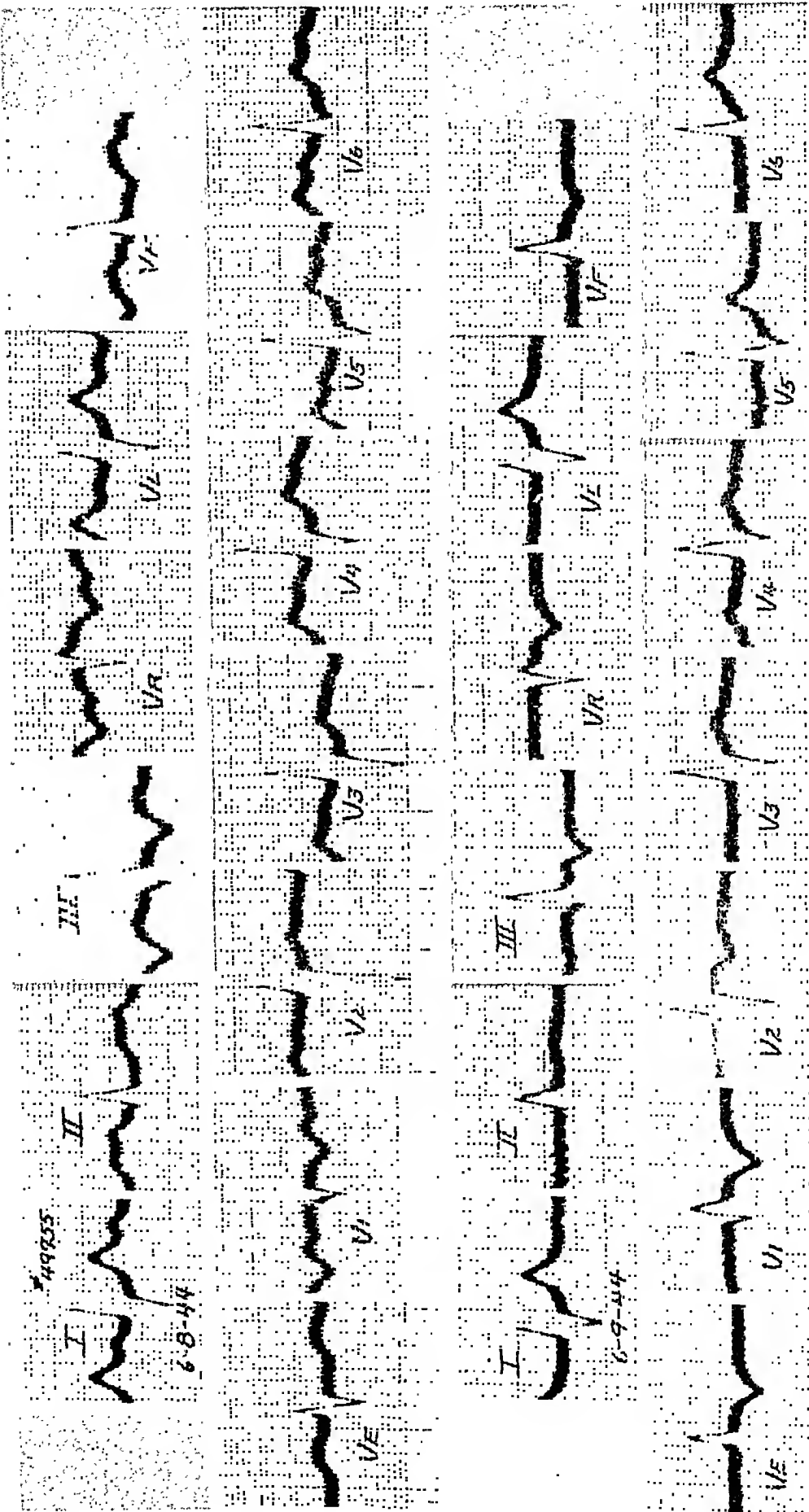


Fig. 9.—Pulmonary embolism.

V₅. There are, however, some striking exceptions to these general rules. We have seen, for example, conspicuous flattening of the T waves in Lead I, terminal inversion of this wave in Lead V_L, and a large pointed positive T wave in Lead III when the complexes of Leads V₁, V₂, and V₃ were diagnostic of infarction and those of Leads V₄, V₅, and V₆ were normal in every respect. More interesting still are those cases in which the complexes of Lead I are diagnostic or very strongly suggestive of anterior infarction while those of the precordial leads are either of the normal type or show only minimal changes of the kind characteristic of this lesion.

The electrocardiograms reproduced in Fig. 10 are those of a man, aged 41 years, who gave a history of severe attacks of chest pain in 1943 and developed a persistent left hemiparesis in May of that year. He had been told that his blood pressure was elevated, but at the time when he was first seen it was only 120/80. The heart was slightly to moderately enlarged; no murmurs were heard. There were no signs of congestive cardiac failure. The extremity curves show conspicuous Q waves and terminal inversion of the T waves in Lead I and Lead V_L. The usual precordial leads are negative except for low R waves preceded by tiny Q waves in V₃ and V₄ and terminal inversion of the T waves in V₃, V₄, and V₅. The leads taken from higher levels, particularly those from the 3rd and 4th intercostal spaces in the left midclavicular and the left anterior axillary line, show considerably more striking changes. The electrocardiograms of this patient differ from those attributed to high lateral infarction in a previous report.²⁵ The latter showed unusually large R and T waves in the leads from the right side of the precordium. Such changes suggest posterior rather than anterior infarction.

Posterior Infarction.—In some cases of posterior infarction in which there are abnormally large Q waves and sharply inverted T waves in Leads II, III, and V_F, the same kind of changes are present in Lead V₆. The leads from the right side of the precordium may, or may not, display unusually large R waves and tall pointed T waves. Tracings of this kind have been ascribed to infarction of the posterolateral wall of the left ventricle.²⁵

The electrocardiogram reproduced in Fig. 11 is that of a man, aged 61 years, who was first seen on June 18, 1944. There was a history of severe chest pain which radiated to both arms in November, 1943. A diagnosis of coronary thrombosis was made at that time and the patient remained in bed for eight weeks. Some days before he was brought to the hospital he had a second attack of chest pain following moderate exertion. A short time after this, tarry stools were noted. At 4:00 A. M. on June 18 he was awakened by severe pain in the region of the left scapula, through the chest, and in the left abdomen. When he was examined some hours later the blood pressure was 70/50, the pulse rate was 130 per minute, and the rectal temperature was 102° F. The heart was enlarged, the heart sounds were faint, and no murmurs were heard. The abdomen was somewhat rigid and tender on the left side. Death occurred at 3:35 P. M. on June 19, shortly after another attack of severe pain in the chest. The location of the infarcted regions disclosed by the post-mortem examination is shown by the sketch reproduced in

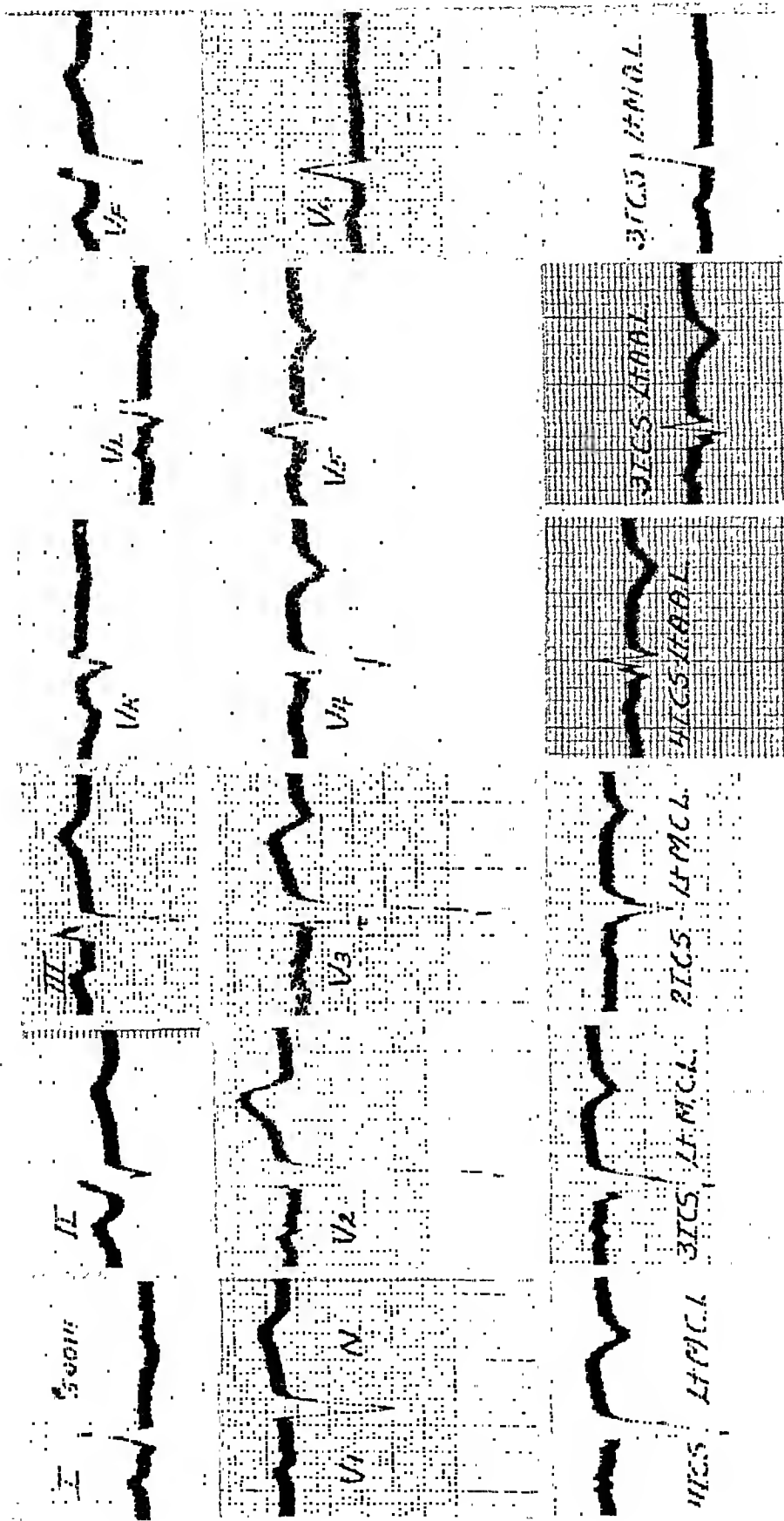


Fig. 10.—Anterior infarction with pronounced signs of infarction in precordial leads from points at higher levels than those from which the standard precordial leads are obtained.

Fig. 12. The autopsy findings included a perforating gastric ulcer complicated by a subphrenic abscess and fibrinopurulent peritonitis.

The electrocardiogram shown in Fig. 13 is that of a man, aged 46 years, who had chest pain of short duration on Sept. 10, 1911. On the following day he had a second attack which lasted one hour. He was then kept in bed, and was told that his blood pressure was 200. He continued to have pain and on September 16 had an unusually severe attack. At the time of the physical examination on the same day, he was still complaining of pain. The blood pressure was



Fig. 11. Postero-lateral infarction.

150/90 and the white blood count was 11,000 per cubic millimeter. The abdomen was distended and tender. The heart was not enlarged, but subsequent roentgenographic studies showed some broadening of the aorta. There was a past history of intermittent claudication, and no pulsation could be felt on palpation of the left dorsalis pedis artery. The patient made a good recovery from the coronary accident.

The first electrocardiograms taken on September 18 were considered within normal limits. There was a slight flattening of the T waves in the limb leads and a slight concavity of the RS-T segment in Leads V_1 and V_2 . A number of tracings

taken during the next few days were of similar form. On September 27, however, there was a sharp dip at the end of the T wave in Lead I. The precordial electrocardiogram of the same date shows large pointed upright T waves in Leads V_1 , V_2 , and V_3 in which these waves had previously been small, and terminal inversion of T in Lead V_6 . More striking inversion of T is present in leads from a high point in the left axilla, from the left posterior axillary line at the level of the fourth costosternal junction, and from the left scapular region. These findings suggest that the infarct was on the posterolateral wall of the left ventricle well toward the base. This case illustrates the desirability of taking serial electrocardiograms when the first tracing is negative and of caution in ruling out infarction on the basis of the absence of characteristic electrocardiographic changes.

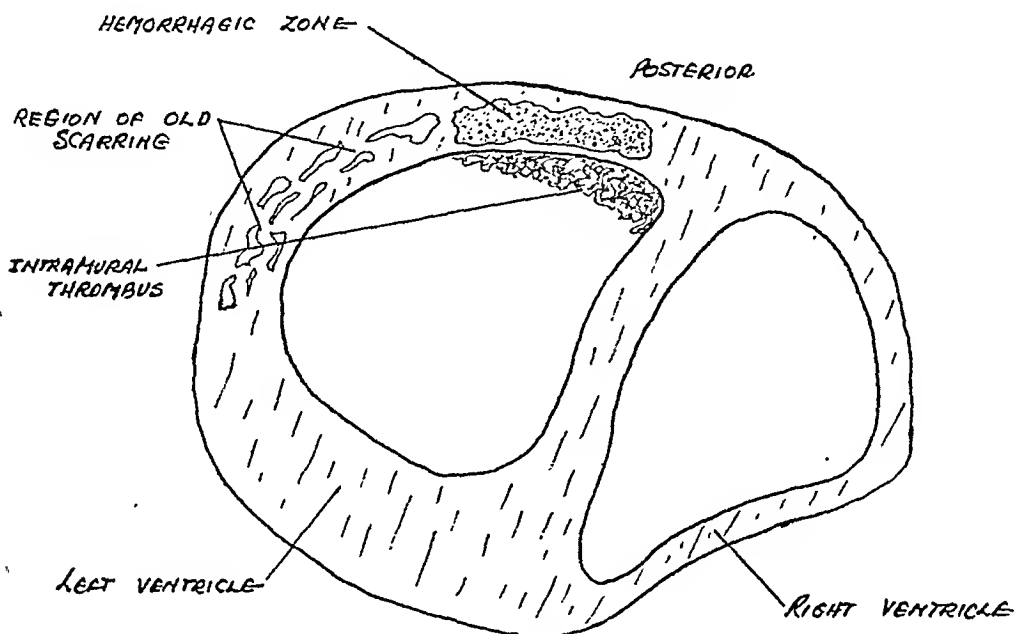
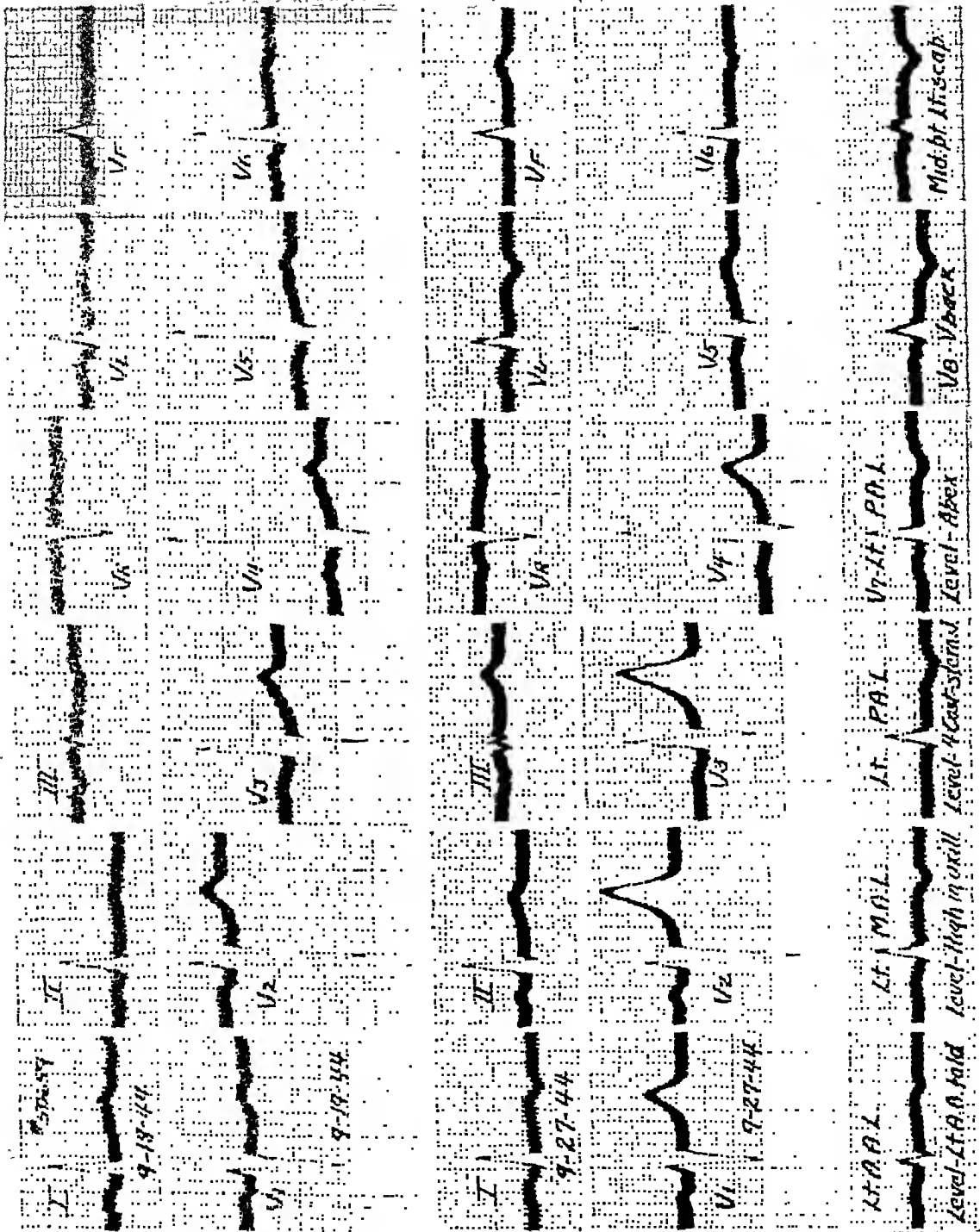


Fig. 12.—Compare with Fig. 11. Location of the infarcted areas found at autopsy.

The electrocardiogram reproduced in Fig. 14 is that of a man, aged 78 years, who was awakened at 2:00 A. M. on Sept. 29, 1944, by severe epigastric pain radiating to the left scapula. The pain was followed by coughing and the expectoration of frothy blood-tinged sputum. When seen at the hospital some hours later, he was cyanotic and the blood pressure was 110/76. On previous examinations the systolic pressure had been in the neighborhood of 150 to 160. The heart was borderline in size; the sounds were extremely faint; no murmurs were heard. Coarse moist râles were audible over the entire lung field. Death occurred about forty-eight hours after the onset of symptoms.

The limb leads are diagnostic of right bundle branch block, but also show large Q waves in Leads II and III and upward RS-T displacement in the last of these leads, which are characteristic of posterior infarction. The precordial leads, however, in addition to the late R waves in Leads V_1 , V_2 , and V_E , which are attributable to right branch block, show pronounced upward RS-T displacement in these same leads and in Leads V_3 and V_4 as well. These findings suggest antero-



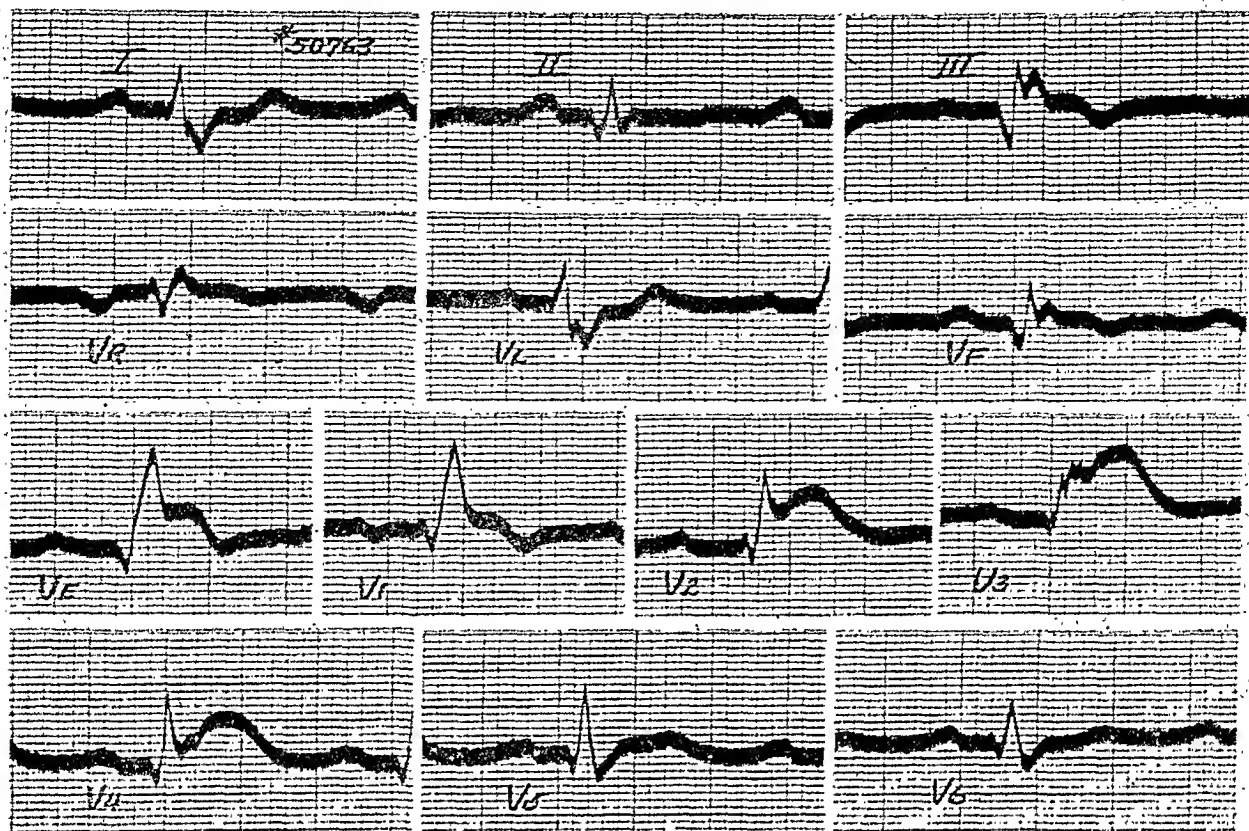


Fig. 14.—Right bundle branch block associated with signs of posterior infarction in the limb leads and signs of anteroseptal infarction in the precordial leads.

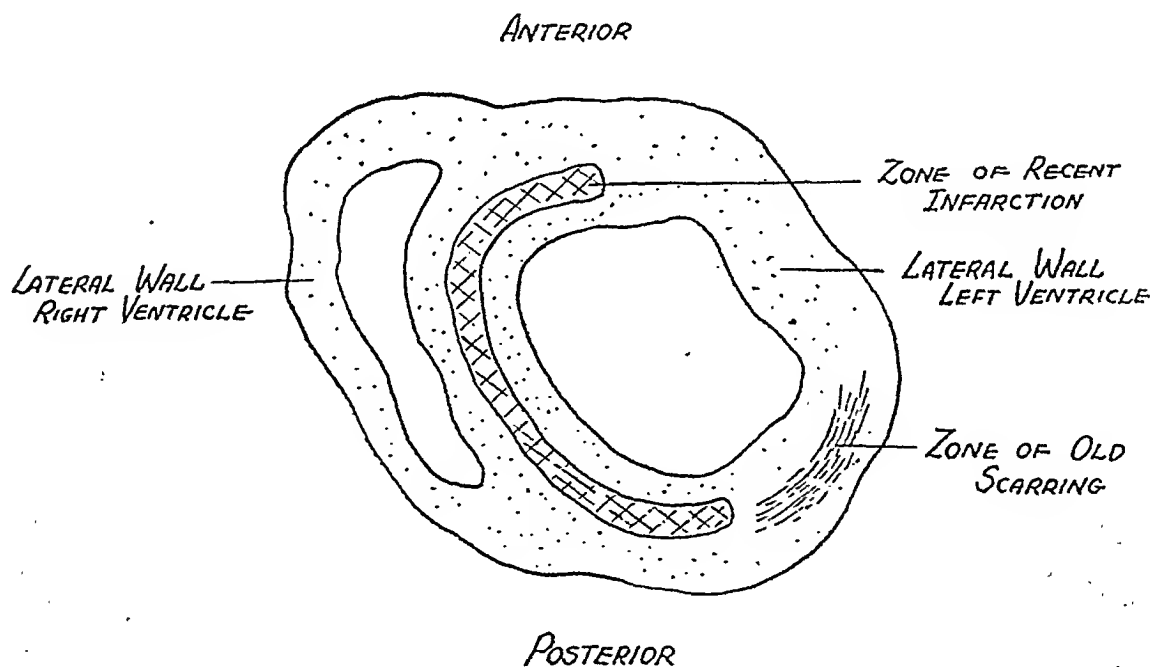


Fig. 15.—Compare with Fig. 14. Location of the infarcted areas found at autopsy.

septal infarction. The location of the infarcted regions disclosed by the post-mortem examination is shown in Fig. 15. Both coronary arteries showed pronounced atherosclerotic changes and the lumen of the anterior descending branch of the left was nearly obliterated. No thrombi were found in these vessels.

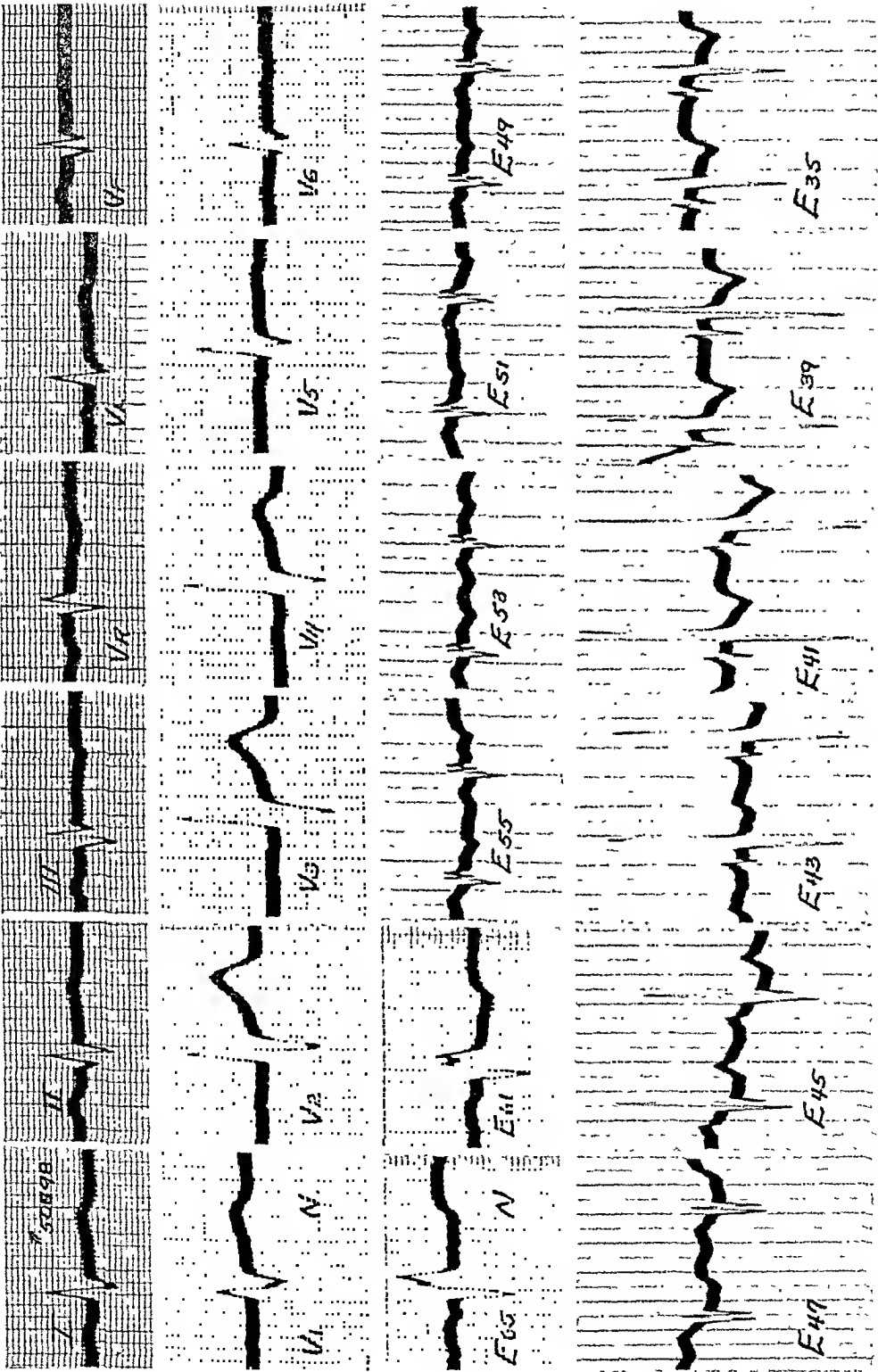


Fig. 16.—Changes suggesting old posterior infarction in a case in which the clinical history made it seem very unlikely that infarction had occurred. The symbol E is used to designate an esophageal lead. The numeral attached to this letter gives the distance (in centimeters) of the exploring electrode from the nares.

The electrocardiograms reproduced in Fig. 16 are those of a man, aged 39 years, who had two spontaneous attacks of anginal pain in June, 1944. The first pain was felt in the region of the lower sternum and persisted throughout the day; it was not particularly severe. The second attack occurred about thirty-six hours later; the pain was under the midsternum and lasted for about thirty minutes. Subsequently, there was mild anginal pain on brisk exertion. Physical examination on Sept. 21, 1944, was negative except for a moderately loud late systolic murmur at the apex. The blood pressure was 128/75. There was nothing in the past history which threw any light on the development of angina pectoris.

The electrocardiogram shows large Q waves in Leads II, III, and V_F and in all of the leads from the ventricular levels of the esophagus. There are also rather prominent Q waves in Lead V_6 . No changes in the T deflections suggesting myocardial infarction are present, but when such changes are present initially they may disappear in the course of three or four months. We consider the electrocardiograms in this case characteristic of old posterolateral infarction, but a diagnosis of infarction could not be made because standard limb leads taken in 1936 during a physiologic experiment showed exactly the same peculiarities as those taken at the time of our examination. We do not know what the correct explanation of these observations may be. We feel, however, that it is imperative to avoid making a clinical diagnosis on the basis of electrocardiographic examination when, after adequate investigation, it is certain that this diagnosis is not supported by the history and other clinical data.

REFERENCES

1. Einthoven, W., Fahr, G., and de Waart, A.: Ueber die Richtung und die manifeste Grösse der Potentialschwankungen im menschlichen Herzen und ueber den Einfluss der Herzlage auf die Form des Elektrokardiogramms, *Arch. f. d. ges. Physiol.* 150: 308, 1913.
2. Lewis, T., Drury, A. N., and Ilescu, C. C.: A Demonstration of Circus Movement in Clinical Flutter of the Auricles, *Heart* 8: 341, 1921.
3. Fahr, G., and Weber, A.: Ueber die Ortsbestimmung der Erregung im Menschlichen Herzen mit Hilfe der Elektrokardiographie, *Deutsches Arch. f. klin. Med.* 117: 361, 1914.
4. Wagner, G.: Physikalische Untersuchungen zum Dreieckschema nach Einthoven, *Zentralbl. f. Herz-u. Gefässkr.* 16: 1, 1924.
5. Johnston, F. D., Kossmann, C. E., and Wilson, F. N.: Unpublished observations.
6. Wilson, F. N., and Herrmann, G. R.: Unpublished observations.
7. Stratton, J. A.: *Electromagnetic Theory*, New York, 1941, McGraw-Hill Book Co.
8. Helmholtz, H.: Ueber einige Gesetze der Vertheilung elektrischer Ströme im körperlichen Leitern mit Anwendung auf die thierisch elektrische Versuche, *Poggendorff's Annalen* 89: 211, 1853.
9. (a) Wilson, F. N., Macleod, A. G., and Barker, P. S.: Electrocardiographic Leads Which Record Potential Variations Produced by the Heart Beat at a Single Point, *Proc. Soc. Exper. Biol. & Med.* 29: 1006, 1932.
(b) Wilson, F. N., Johnston, F. D., Macleod, A. G., and Barker, P. S.: Electrocardiograms That Represent the Potential Variations of a Single Electrode, *AM. HEART J.* 9: 447, 1934.
10. Burger, R., and Wuhrmann, F.: Ueber das elektrische Feld des Herzens. II. Mitteilung, *Cardiologia* 3: 139, 1939.
11. Arrighi, F.: Personal communication, 1942.
12. Arrighi, F.: *El Eje Electrico del Corazon en el Espacio*, Facultad de Ciencias Medicas, Univ. Nacional de Buenos Aires, Buenos Aires, 1938.

13. Eckey, P., and Fröhlich, R.: Zur Frage der unipolaren Ableitung des Elektrokardiogramms, *Arch. f. Kreislaufforsch.* 206: 181, 1938.
14. Burger, R.: Ueber das Elektrische Feld des Herzens. I. Mitteilung, *Cardiologia* 3: 56, 1939.
15. Wolferth, C. C., and Livezey, M. M.: A Study of the Methods of Making So-Called Unipolar Electrocardiograms, *AM. HEART J.* 27: 764, 1944.
16. Cole, K. S., and Curtis, H. S.: Electric Impedance of Nitella During Activity, *J. Gen. Physiol.* 22: 37, 1938.
17. Lewis, T., and Rothschild, M. A.: The Excitatory Process in the Dog's Heart. Part II. The Ventricles, *Phil. Tr., Lond. Series B* 206: 181, 1915.
18. Wilson, F. N., and Herrmann, G. R.: Bundle Branch Block and Arborization Block, *Arch. Int. Med.* 24: 153, 1920.
19. Wilson, F. N.: The Distribution of the Potential Differences Produced by the Heart Within the Body and at Its Surface, *AM. HEART J.* 5: 599, 1930.
20. Wilson, F. N., Wishart, S. W., and Herrmann, G. R.: Factors Influencing Distribution of Potential Differences, Produced by Heart Beat, at Surface of Body, *Proc. Soc. Exper. Biol. & Med.* 23: 276, 1926.
21. Macleod, A. G., Wilson, F. N., and Barker, P. S.: The Form of the Electrocardiogram. I. Intrinsicoid Deflections in Animals and Man, *Proc. Soc. Exper. Biol. & Med.* 5: 599, 1930.
22. Wilson, F. N., Macleod, A. G., and Barker, P. S.: The Order of Ventricular Excitation in Human Bundle Branch Block, *AM. HEART J.* 7: 305, 1932.
23. Wilson, F. N., Macleod, A. G., and Barker, P. S.: The Potential Variations Produced by the Heart at the Apices of Einthoven's Triangle, *AM. HEART J.* 7: 207, 1931.
24. Kellogg, O. P.: *Foundations of Potential Theory*, New York, 1943, Frederick Ungar Publishing Co.
25. Wilson, F. N., Johnston, F. D., Rosenbaum, F. F., Erlanger, H., Kossmann, C. E., Hecht, H., Cotrim, N., Menezes de Oliveira, R., Scarsi, R., and Barker, P. S.: The Precordial Electrocardiogram, *AM. HEART J.* 27: 19, 1944.
26. Durant, T., Ginsburg, M. D., and Roesler, H.: Transient Bundle Branch Block and Other Electrocardiographic Changes in Pulmonary Embolism, *AM. HEART J.* 17: 423, 1939.

THE EFFECT OF SALICYLATES ON ACUTE RHEUMATIC FEVER

LIEUTENANT COLONEL HARRY A. WARREN, M.C., LIEUTENANT COLONEL C. S.
HIGLEY, M.C., AND MAJOR F. S. COOMBS, M.C., ARMY OF
THE UNITED STATES

THE most important problem in the treatment of acute rheumatic fever is the prevention of organic heart disease. To effect this it is essential that the rheumatic inflammatory reaction be suppressed in the minimum of time and that polycyclic attacks of rheumatic fever be prevented. If rheumatic attacks were always monocyclic and short lived, severe cardiac damage would rarely occur. For many years salicylates have been used in rheumatic fever in an attempt to attain these objectives. There is general agreement on the rapid antipyretic action of salicylate and on the efficient alleviation of pain and swelling of the joints with salicylate therapy. Whether salicylates prevent polycyclic attacks or reduce the incidence of permanent cardiac damage has been disputed for years.

In 1914, Miller¹ reviewed the literature on the action of salicylates in acute articular rheumatism. He found that with salicylate therapy pain was relieved in an average of 5.3 days; without salicylates pain persisted for 13.4 days. Relapses occurred in 30.3 per cent of the 1,258 patients receiving salicylates, but only 6 per cent of the 974 patients who did not receive salicylates had recurrence of their symptoms. There was no difference in the length of hospital stay in the two groups. Miller quotes Pribram on the incidence of cardiac complications: cardiac damage developed in 28.8 per cent of patients on salicylate and in 23.4 per cent of patients not receiving salicylate. During the period reviewed, Miller states that 15 to 20 grains of sodium salicylate every two or three hours was considered a moderate dose and many physicians gave as much as 300 grains a day. In 1918, Hanzlik, Scott, and Gauchat² in a study of the specific effect of salicylates on rheumatic fever concluded that while salicylate is effective it is not specific and that other drugs will produce the same results though perhaps not so consistently. They stated that salicylate was no more than a symptomatic remedy. They found no reduction in the occurrence of endocarditis with salicylate therapy. In 1925, Swift³ stated that salicylates had a favorable effect on the exudative phase of rheumatic fever but that it failed to influence markedly the proliferative lesions. He felt that this explained why salicylates had no effect on chorea and did not prevent valvular lesions in patients receiving full dosage. He did emphasize that these drugs were of great assistance in reducing the fever and con-

Presented in part before the Eighteenth Annual Meeting of the Central Society for Clinical Research, Chicago, Ill., Nov. 2 and 3, 1945.
Received for publication Jan. 31, 1946.

trolling the "toxic state." The tendency to lose weight was less marked in patients receiving salicylates. With the reduction in fever and toxicity there was a lowering of the heart rate. Swift pointed out that if salicylate eliminated the edema from the valves, as it does from the periarticular tissues, some of the traumatic injury to the endocardium might be eliminated. He emphasized the importance, both to the physician and the patient, of continued care, even after all symptoms are relieved by salicylate therapy, as otherwise the patient may in the end suffer more permanent injury than if he were untreated. In 1933, Graef, Parent, Zitron, and Wyckoff⁴ reported a series of 105 cases of acute rheumatic fever treated only with opiates and local therapy to the affected joints. They stressed the tendency of the acute manifestations of rheumatic fever to subside spontaneously and often rapidly.

In 1943, Coburn⁵ reopened the problem of salicylate therapy in rheumatic fever in his report of 101 cases treated with varying amounts of sodium salicylate. Sixty-three patients received only small doses of the drug, and 21 developed organic heart disease. Thirty-eight received 10 Gm. or more of sodium salicylate daily, and none of these developed heart disease. Coburn administered sodium salicylate by mouth and also intravenously in doses of 10 to 20 Gm. daily. He felt that by giving the medication by vein, a more rapid and sustained rise in the plasma concentration of the drug was obtained. His studies were controlled by estimations of the plasma level. He concluded that a plasma salicylate level of at least 35 mg. per 100 c.c. may be required to suppress the rheumatic reaction and that plasma levels below 20 mg. per 100 c.c. may be sufficient to relieve symptoms while masking a progressive inflammatory process.*

Hanzlik⁶ credits Mendel with the first use of intravenous salicylate in 1904. Hanzlik⁶ quotes Matta, Lesne, Gilbert, Coury, and Bernard as using this method of administration. These clinicians claimed certain advantages in the intravenous method over the oral route: namely, the avoidance of gastric disturbances, emesis, and side reactions in general; more rapid absorption of the drug; and finally the prevention of cardiac complications. Coburn has revived the interest in this method and claims that a more rapid elevation of the blood salicylate is obtained and that the patient is more quickly brought under control.

McEachern⁷ has reported his results in 350 cases of acute rheumatic fever treated between November, 1943, and June, 1944. Toxic reactions were frequent with intravenous medication and minimal in the orally treated group. Cardiac sequelae were present in both groups. He concluded that oral administration of 10 to 16 Gm. of sodium salicylate was the most satisfactory method of treatment. Taran and Jacobs⁸ concluded that intravenous salicylate offered no advantages in treatment and that the technical difficulties and annoying symptoms outweighed the possible benefits of a more rapid rise in the plasma salicylate level.

Hanzlik,⁶ Goodman and Gilman,⁹ and, more recently, P. K. Smith¹⁰ have concluded that intravenous administration is unwarranted because of the rapid and almost complete absorption of sodium salicylate from the gastrointestinal tract. Smith has shown that peak plasma levels are reached about one hour after

*Coburn introduced the term *gamma per cubic centimeter* for salicylate levels. We feel that such terminology may be confusing and prefer to retain the more familiar *milligram per 100 c.c.* for the sake of clarity.

oral administration. Hanzlik states that the advantages claimed by the supporters of the intravenous method are unsupported by any evidence and that, when administered in this way, salicylate may cause considerable damage to the heart and other important organs.

In June, 1945, Keith and Ross¹¹ reported their results in the treatment of two groups of patients with acute rheumatic fever in the Royal Canadian Navy. The sedimentation rate returned to normal in an average of four weeks in a group of 70 patients receiving 10 to 13.3 Gm. of salicylate per day and in four and one-half weeks in 33 patients receiving 0 to 1.7 Gm. a day. Three patients in the low dosage group and five in the high salicylate dosage group developed heart disease. Five patients who had pre-existing heart disease showed progression, two in the low and three in the high salicylate group. They could not conclude that large amounts of salicylates were of any more benefit than small doses. Taran and Jacobs⁸ recently reported their experience with large doses of salicylate. They concluded that large doses of salicylate brought about prompt and effective response both in patients with polyarthritis without carditis and in those patients with carditis. They state that if therapy is not instituted promptly activity continues for many weeks. Small doses of salicylate in their experience had no more effect than no salicylate at all in patients with carditis. Murphy,¹² in a recent report of careful studies in twelve patients receiving large doses of salicylate, questions the usually accepted view that salicylates promote the subsidence of rheumatic joint inflammation. In several patients characteristic lesions developed in a variety of sites during the course of heavy salicylate therapy. It is obvious that there is still no agreement as to the efficiency of salicylate in preventing cardiac damage or the ability of large doses to reduce rheumatic activity more quickly than small amounts.

METHODS OF STUDY

We have observed 186 cases of acute rheumatic fever in young adults between November, 1942, and September, 1945. These patients have been observed under three different therapeutic regimes. Some have been treated with small doses of salicylate given only to relieve symptoms. Others received large doses by mouth until all evidence of rheumatic activity had subsided. A third group received sodium salicylate intravenously for one week and then large oral doses. We wish to report our experience with these three types of treatment considering the effect on the length of rheumatic activity, on polycyclic attacks, on pericarditis, and on the occurrence of permanent cardiac damage.

The diagnosis in each case was carefully determined and in all cases the criteria established by Jones¹³ were applied. In each case, before therapy was started, a complete history was taken and a physical examination was made; other studies made on each patient included an electrocardiogram, an x-ray of the heart, hemoglobin determination, erythrocyte count, leucocyte and differential counts, urine examination, and erythrocyte sedimentation rate. A twenty-four hour period of observation was used in most cases before starting therapy and in a few cases three days to two weeks of observation took place

before the diagnosis was accepted and therapy was started. Routine urine examinations were done once weekly. Certain patients with acute rheumatic fever were not included in this study, because of the occurrence of purulent complications which would influence the sedimentation rate and fever. The patients with pneumonitis are included except where sputum examination and the clinical course indicated that it was not of rheumatic origin. In all cases studied from November, 1943, on, sedimentation rates were done two or three times weekly for two to four weeks and then once weekly; electrocardiograms were taken two or three times weekly for two weeks and then once weekly. The patients studied in 1942 and 1943 received these tests less often. In 1942 and 1943 the Wintrobe method was used in determining the sedimentation rate, but after January, 1944, the Westergren method was used, without correction for the cell volume. This was not necessary as no significant anemias were encountered. Hemoglobin, red blood cell counts, and leucocyte counts were done twice monthly. In many of the later cases antistreptolysin determinations were done to assist in establishing a diagnosis. All but two of the patients were men. The age range was 18 to 40 years; 70 per cent were under 25 years and 87 per cent were under 30 years of age. There were no significant differences in the age composition of the three treatment groups. Fifty-one per cent of those receiving small doses and 39 per cent of those receiving large doses had a history of previous rheumatic fever. Pre-existing rheumatic valvular heart disease was present in 12.5 per cent of the small dose group and in 5 per cent of the large dose group. The differences in these proportions are not statistically significant.

Eighty-eight patients were treated with small doses, ranging from 2 to 7 Gm. a day. The drug was given until nausea or tinnitus developed or until relief of symptoms was obtained, and the dose was reduced markedly or it was eliminated entirely when the pain and fever had subsided, regardless of the level of the sedimentation rate. Sodium bicarbonate was usually given in equal doses. The medication was given four to eight times during the day from 8:00 A. M. to 10:00 P. M. In some cases acetyl salicylic acid was used and in others sodium salicylate. Sixty-four patients treated by this method were admitted during the winter of 1942-1943, 17 in the winter of 1943-1944, and 7 in 1944-1945.

Fifty patients were treated with 10 to 16 Gm. of sodium salicylate per day by mouth. The medication was divided into equal doses and given at four-hour intervals throughout the twenty-four hours. Sodium bicarbonate was given when necessary to reduce gastric irritation and to prevent toxic reactions. Plasma salicylate determinations were done several times weekly and the dosage was adjusted to maintain levels of 35 to 45 mg. per 100 cubic centimeters. The salicylate was continued in this dosage until the sedimentation rate had maintained a normal level for at least two weeks. If the sedimentation rate rose after salicylate was stopped, the drug was again given in the same dosage until the sedimentation rate again remained normal for two weeks. In some cases salicylate was omitted for several days because of a high plasma level or because of toxic symptoms.

Forty-eight patients were given 10 Gm. of sodium salicylate in 1,000 c.c. of normal saline daily for seven days. The infusion was administered slowly over a six to eight-hour period. In several cases doses of 14 and 20 Gm. were given for one or several days because of continued symptoms. The day following the last intravenous injection these patients were started on 10 to 16 Gm. of sodium salicylate by mouth daily and continued as in the large oral dosage group. Plasma salicylate levels were determined several times weekly in this group. The patients treated with large doses of sodium salicylate were observed from March, 1944, through the remainder of the study.

THE EFFECT ON THE SEDIMENTATION RATE

The erythrocyte sedimentation rate, while a nonspecific test, has been accepted as a sensitive indicator of rheumatic activity. Most authorities agree that physical activity should be limited until the sedimentation rate has reached a normal level. The comparative effects of the three methods of treatment on the sedimentation rate should be indicative of the relative effect on rheumatic activity.

The sedimentation rate may show wide fluctuations in acute rheumatic fever as the inflammatory process varies in intensity. A certain number, those with monocyclic attacks, will show a prompt drop in the rate to a normal level (Fig. 1, Patient H. P.). If these patients are used to show the effect of salicylate therapy it will indicate a marked effect. Some patients may show an apparent response but then continue with lower but abnormal sedimentation rates suggesting a repression of rheumatic activity by salicylate (Fig. 1, Patient A. E.). Other patients will have polycyclic attacks with recurring waves of activity. Here, if salicylate is given with the rate elevated, it will show an effect as the rate falls. If it is then omitted the rise in rate suggests that salicylate was stopped too quickly. However, in Fig. 2, Patient A. D., it is seen that this may occur regardless of salicylate therapy with so-called adequate blood levels. Some patients show continuous rheumatic activity with wide fluctuations of the sedimentation rate uninfluenced by adequate plasma salicylate levels (Fig. 2, Patient R. N.). Graef, Parent, Zitron, and Wyckoff⁴ have stressed these variations in duration of activity and the tendency of acute manifestations to subside spontaneously in the course of untreated rheumatic fever. Ernstene¹⁴ found that frequently the sedimentation rate increased slightly after stopping salicylate and then dropped promptly to the previous level.

In order to take into consideration these fluctuations in rheumatic activity and the effect of salicylate therapy on the disease, we have added the days in which the sedimentation rate was above 20 mm. per hour to obtain the total days elevation for each case. An average number of days of elevated sedimentation rate was then determined for each treatment schedule. These averages have been subjected to statistical analysis to determine the significance of the differences under the three plans of treatment.

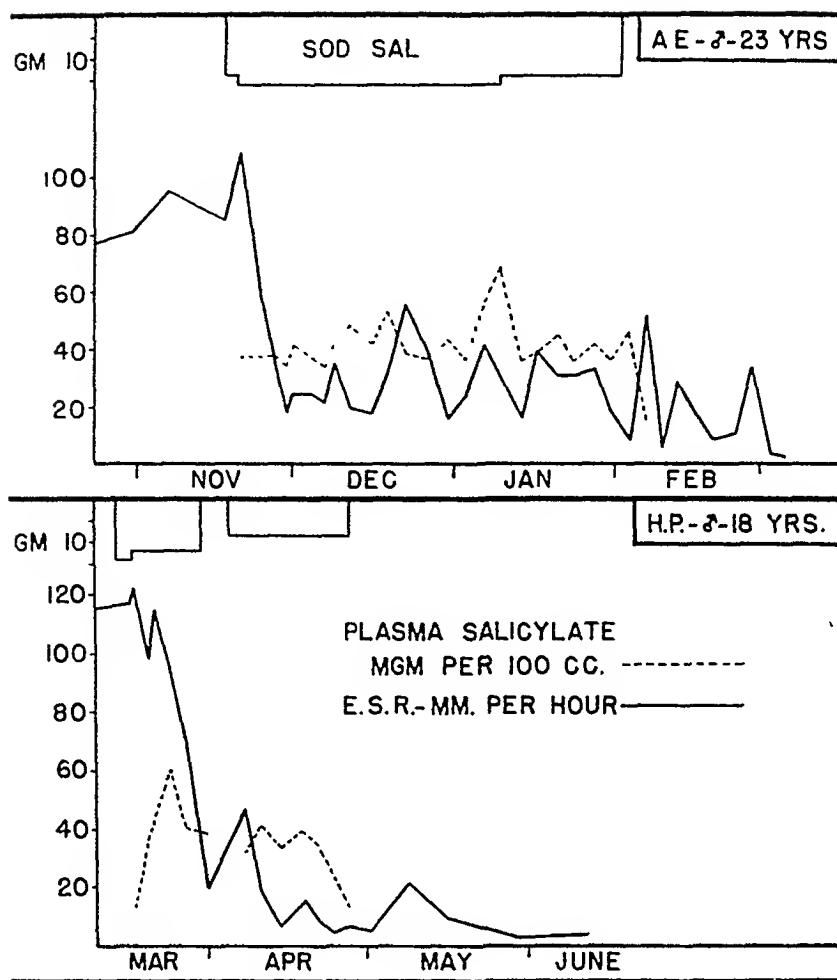


Fig. 1.—Patients A. E. and H. P. The chart shows the relationship of the erythrocyte sedimentation rate, plasma salicylate levels, and the dose of sodium salicylate by mouth.

In an effort to separate the severe cases from those with mild rheumatic inflammation, we have divided the cases into two groups; those with sedimentation rates of 60 mm. per hour or less and those with higher rates.

One hundred twenty-six cases were observed where the highest sedimentation rate was over 60 mm. per hour. Table I shows the average number of days of elevated sedimentation rates in the three treatment groups. There is a range of ten days between the large oral dosage and the intravenous groups with the small dose group falling between the two. Statistically, the difference of these means is not significant and we can conclude that in these three groups there was no more rapid reduction of rheumatic activity with large than with small amounts of salicylate.

Sixty cases were studied where the highest sedimentation rate was under 61 mm. per hour. Fifty-one patients received small doses of salicylate and had elevated sedimentation rates for an average of 35.2 days. There were only four

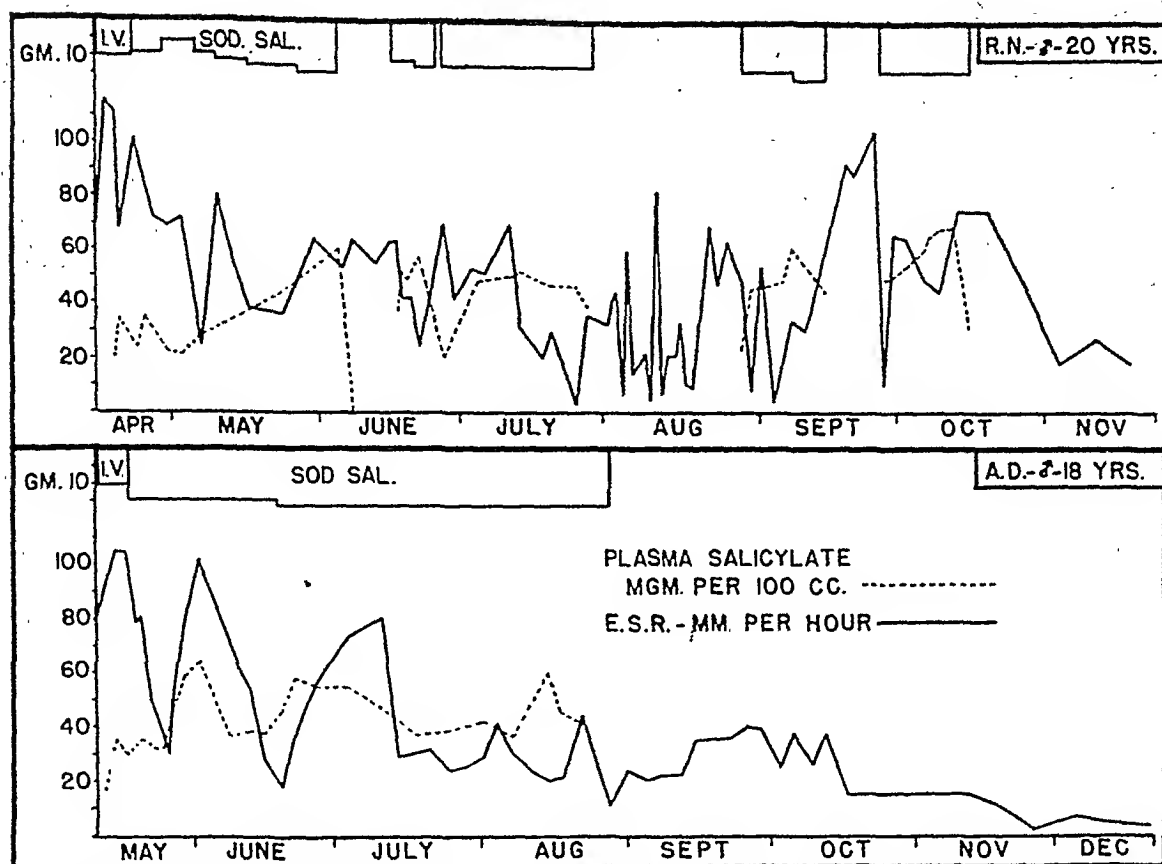


Fig. 2.—Patients R. N. and A. D. The chart shows the relationship of the erythrocyte sedimentation rates, plasma salicylate levels, and the dose of sodium salicylate intravenously and by mouth.

TABLE I. THE EFFECT OF SALICYLATE ON THE ERYTHROCYTE SEDIMENTATION RATE

	CASES	MEAN DAYS ELEVATED E. S. R.
<i>E. S. R.* over 60 mm./hour</i>		
Small oral.....	37	58.7
Large oral.....	45	51.3
Intravenous.....	44	61.4
<i>E. S. R. under 60 mm./hour</i>		
Small oral.....	51	35.2
Large oral.....	5	36
Intravenous.....	4	27.8
<i>All Cases</i>		
Small oral.....	88	45.1
Large oral.....	50	49.8
Intravenous.....	48	58.6
Total large and oral and intravenous.....	98	54.1

*E. S. R.=erythrocyte sedimentation rate.

patients who received intravenous therapy and five who received large oral doses in this group, too few to offer any accurate comparison in effectiveness of therapy (Table I).

Table I also shows the consolidated data for all cases observed, both high and low sedimentation rate groups. Here the greatest difference between the means is 13.5 days, between the small dose and the intravenous therapy group. Here again, by statistical analysis there is no significant difference between the average days of elevated sedimentation rate for the three treatment groups. If we consider all the large dosage patients, both oral and intravenous, the average number of days of elevated sedimentation rate is 54.1. The difference between this average and that for the small dose group is nine days, again not a statistically significant difference. The median for the small dose group was just over six weeks while the median for the large dosage group was also six weeks.

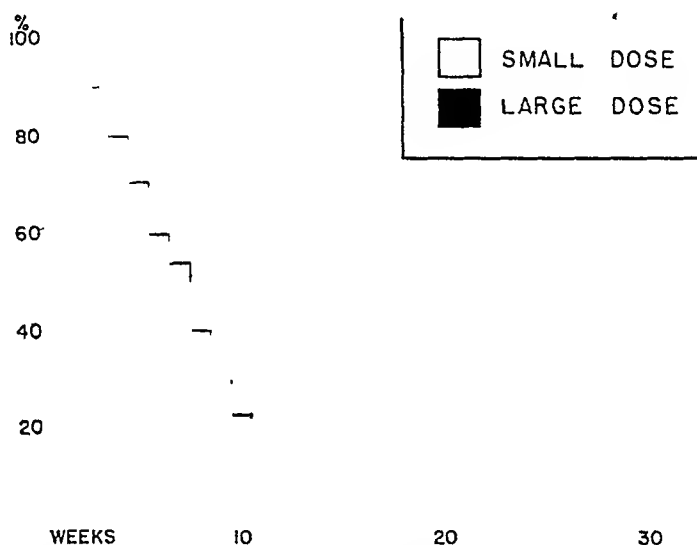


Fig. 3.—The percentage of cases with elevated sedimentation rates, by weeks, under treatment with small and with large doses of salicylate.

The higher average days resulted from seven patients with sedimentation rates which remained elevated for more than twenty-two weeks. Fig. 3 shows the proportion of the total small and large dose groups with elevated sedimentation rates in consecutive weeks of observation. Here it can be seen that actually there is no real difference. The two curves follow each other almost exactly except for those cases with prolonged activity which perhaps by chance occurred only in the last two seasons and were treated with large doses. In any event from our data it is seen that large doses of salicylate are no more effective than small doses in reducing an elevated sedimentation rate.

THE EFFECT ON FEVER

The data on the effect on the temperature are based on oral temperature as recorded by the ward nurses in a routine manner. Temperatures were taken four times daily during the period of acute illness and then twice daily, at 8:00 A. M. and 4:00 P. M. One hundred seventy-one patients showed a temperature of

TABLE II. THE EFFECT OF SALICYLATE ON THE NUMBER OF DAYS OF FEVER

	CASES	MEAN DAYS OF FEVER
Small oral.....	82	11.63
Large oral.....	44	3.77
Intravenous.....	45	4.57
Total large, oral and intravenous.....	89	4.16

99.2° F. or more on at least one occasion. Table II shows the average number of days of fever in the three treatment groups. The greatest difference is 7.8 days between the small and the large oral treatment groups. Between the intravenous and the small therapy group is a difference of seven days. By statistical analysis both of these differences are significant, and we can conclude that large doses of salicylate will reduce the temperature to normal more quickly than small doses. It is also evident that oral, large dose therapy is more effective than the intravenous method. Fig. 4 shows the proportion of the small and total large dose (both oral and intravenous) groups with fever in consecutive days of observation. Here again, the advantage of using large doses of salicylate in eliminating the febrile reaction is evident.

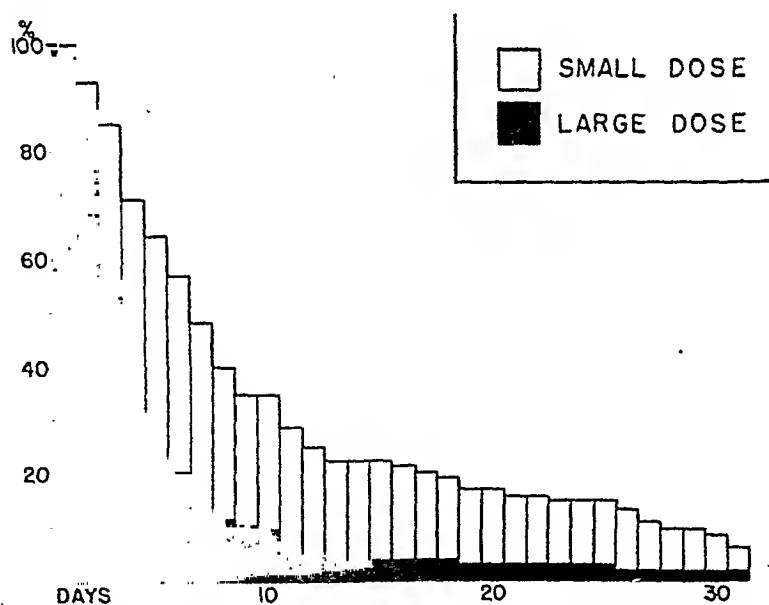


Fig. 4.—The percentage of cases with fever, by days, under treatment with small and large doses of salicylate.

THE EFFECT ON POLYCYCLIC ATTACKS

Coburn⁵ has pointed out the difficulty in determining whether any form of treatment has a therapeutic effect in rheumatic fever. About 20 per cent of young adults may be expected to have monocyclic attacks and recover spontaneously in about three weeks with symptomatic therapy. We have tabulated the data on polycyclic attacks in our group and included every patient who showed a

TABLE III. THE EFFECT OF SALICYLATE ON POLYCYCLIC RHEUMATIC FEVER

	TOTAL CASES	POLYCYCLIC CASES	%
<i>E. S. R. over 60 mm./hour</i>			
Small oral.....	37	19	51.3
Large oral.....	45	28	62.1
Intravenous.....	44	28	63.6
<i>E. S. R. under 60 mm./hour</i>			
Small oral.....	51	16	31.2
Large oral.....	5	2	
Intravenous.....	4	2	
<i>All Cases</i>			
Small oral.....	88	35	39.8
Large oral.....	50	30	60
Intravenous.....	48	30	62.5
Total large, oral and intravenous.....	98	60	61.3

secondary elevation in sedimentation rate after the rate had reached a normal level (Table III). In some patients there were, in addition, clinical signs and symptoms indicating rheumatic activity. Thirty-five patients, 39.8 per cent of all those receiving small doses, showed such polycyclic manifestations. Thirty patients, 60 per cent of all patients receiving large oral doses, and 30 patients, 62.5 per cent of all receiving intravenous therapy, showed polycyclic attacks. The difference of these means is statistically significant. In our experience large dose therapy does not reduce the occurrence of polycyclic attacks. It is interesting to note that Miller,¹ in his review in 1914, found a similar effect with salicylate therapy. Of the patients of his series receiving salicylate, 30.3 per cent had relapses while only 6 per cent of those not receiving the drug suffered such polycyclic attacks.

THE EFFECT ON VALVULAR HEART DISEASE

The most important factor in determining the efficacy of various types of therapy is the prevention of valvular heart disease. This is a difficult problem to evaluate in a short study such as this. To be certain one should re-examine these patients several years after the attack of rheumatic fever. The problem of the evaluation of a systolic apical murmur is an important aspect of this question. When a patient is admitted to the hospital with an aortic diastolic

or mitral systolic murmur it is frequently impossible to say how long these murmurs have been present. As a rule, it can be assumed that the murmurs were present before. Furthermore, it is difficult to tell whether the present attack has produced additional cardiac damage or not. We have used Levine's¹⁵ method of grading systolic murmurs throughout this study. Levine states that several observers will vary no more than one grade in classifying murmurs under this system so that a variation of two grades indicates an actual change. For example, a progression from a Grade 1 to a Grade 3 systolic murmur is evidence of actual change in volume of the murmur and, unless associated with elevation of temperature and tachycardia, can be interpreted as evidence of an organic change. Increase in cardiac size under observation is another evidence of increased cardiac damage.

Due to the limited period of observation, any data on the development of cardiac damage we now have are obviously incomplete. However, we can answer the question of the development of cardiac damage with Coburn's large dose method. Fourteen patients in the entire series developed evidence of organic heart disease or showed increased damage of pre-existing heart disease (Table IV).

TABLE IV. THE EFFECT OF SALICYLATE ON THE DEVELOPMENT OF VALVULAR HEART DISEASE

	SMALL DOSE	LARGE DOSE
Aortic insufficiency	2 cases	2 cases
Mitral stenosis	1 case	2 cases
Probable mitral insufficiency	3 cases	3 cases

There were seven patients who developed new cardiac murmurs or showed evidence of increased damage of pre-existing heart disease while receiving large doses of salicylate. Five were given large doses by mouth and two received intravenous therapy. Five of these men had a past history of rheumatic fever. There were two patients who developed aortic insufficiency, one with a past history of rheumatic fever and one without such a history. One received intravenous therapy and one oral. There is no question but that these two men developed valvular heart disease while receiving large doses of salicylate. Two patients receiving large oral doses developed mitral stenosis under observation where no presystolic murmur had been heard on admission. Both patients, however, had a past history of rheumatic fever. The remaining three men were admitted with no cardiac murmurs. They developed persistent Grade 2 apical systolic murmurs. All three gave a past history suggesting previous rheumatic fever.

There were also seven men receiving small doses of salicylates who developed organic heart disease or showed signs of increased damage of an old lesion. Here again two patients developed aortic insufficiency, neither man having a past history of rheumatic fever. One patient developed a presystolic apical murmur and showed an increase in the intensity of a pre-existing apical systolic

murmur. Two patients developed persistent Grade 2 apical systolic murmurs where none existed on admission. Only one of these men had a past history of rheumatic fever. The sixth man on admission had a soft Grade 1 apical systolic murmur which progressed to a rough Grade 3 murmur by the time of discharge. The seventh patient was admitted with mitral stenosis and insufficiency and auricular fibrillation of long standing. He had a mild attack of rheumatic fever but there was possible further cardiac enlargement as the transverse cardiac diameter by x-ray examination increased one centimeter. All of these patients had received small amounts of salicylate but had remained on limited physical activity until the sedimentation rate had remained at a normal level for at least several weeks.

We can conclude, then, that large doses of salicylate will not prevent the occurrence of valvular heart disease or the progression of pre-existing cardiac damage. In our experience there was the same incidence of heart disease in the two groups under observation. Because of the short period of observation, we are not in a position to state that either one or the other method of therapy will lessen cardiac damage.

THE EFFECT ON PERICARDITIS

It is probable that large amounts of salicylate will relieve the joint pain and discomfort more quickly than small doses. We have no statistical data on this aspect of the problem but in using large doses we had little or no difficulty in relieving the symptoms within one to three days. A more certain test of this is the effect on acute pericarditis. There were three cases with acute pericarditis treated by intravenous therapy and one treated with large oral doses of salicylate. Three occurred in the winter of 1944 and one occurred in 1945. The longest period of elevated sedimentation rate was thirty-three days; the average was twenty-six days. The longest period of fever was six days; the average was four. One of these patients developed aortic insufficiency. However, the effect of large dose salicylate therapy was striking. There was rapid subsidence of all joint and chest pain and fever. This was in marked contrast to the cases of pericarditis of the previous season which were treated with small doses of salicylate. Two of these four patients received sulfadiazine because of the presence of pneumonitis and pericarditis and the possibility of a bacterial infection. One of the two also received penicillin for thirty-six hours. In each case there was no effect from the antibiotics but a prompt response to salicylate.

In the fall and winter of 1942-1943, we had seven cases of acute pericarditis treated with small doses of salicylate. The average period of elevation of the sedimentation rate in this group was forty-four days with a range of fifteen to seventy-seven days. Fever was maintained for as long as thirty-four days in one case; the average was twenty-one days. Several of these boys were acutely ill for several weeks. Two of the seven are not included in the averages given because of the development of complications which would influence sedimentation rate and fever. One died in cardiac failure; this was our only death from acute rheumatic fever. Post-mortem examination showed complete obliteration of

the pericardial cavity, multiple areas of pulmonary infarction, and thrombophlebitis of the prostatic venous plexus. The second patient developed an acute empyema during the course of his rheumatic fever, which necessitated thoracotomy and prolonged drainage.

It would appear from our experience that the use of large amounts of salicylate will relieve the symptoms and cause more rapid subsidence of acute pericarditis than will small doses. This in itself would be a definite factor in support of large doses. However, we had only four patients treated with large doses. Moreover, the two groups did not occur in the same season, and it is well known that rheumatic fever varies in severity from one season to another. Despite these criticisms, we have been impressed with the prompt control of pericarditis with large dose therapy.

THE EFFECT ON THE P-R INTERVAL

The occurrence of a prolonged P-R interval in the electrocardiogram is accepted as the most frequent and important electrocardiographic manifestation of acute rheumatic fever. The effect on this sign of cardiac involvement would be helpful in evaluating the efficiency of salicylate therapy. Wyckoff, DeGraff, and Parent¹⁶ have reported careful studies on this problem in eight patients receiving salicylate and ten receiving no therapy. They found that the P-R interval showed wide and inconstant variation uninfluenced by salicylate in doses of 8 Gm. per day. For accurate appraisal of this phase of the problem electrocardiograms should be taken daily. Many of the patients studied in 1943 did not have frequent electrocardiograms. In some cases three weeks elapsed between tracings. However, by presenting our data by weeks some information can be deduced. A total of 47 patients showed a prolonged P-R interval of over 0.22 seconds, or A-V dissociation. Seventeen patients receiving small doses of salicylate showed prolonged P-R intervals and 52.9 per cent of them showed a normal P-R interval by the end of two weeks. However, many of these patients did not have electrocardiograms at intervals close enough to allow accurate evaluation. Five of the patients receiving small doses, whose tracings were taken frequently, required an average of ten days for the P-R interval to reach normal. Eighty per cent had a normal P-R interval at the end of one week. In 81.2 per cent of those receiving large oral doses and in 78.5 per cent of those receiving intravenous therapy the P-R intervals had returned to normal at the end of two weeks. While our data are not sufficient to conclude unequivocally that small doses are as efficacious or more so than large doses, they suggest certainly that there is no apparent advantage in intravenous therapy over large oral medication in the effect on the P-R interval changes.

DISCUSSION

There is no danger in giving such large doses if the signs of toxicity are known and carefully appraised. Tinnitus and diminished hearing are practically universal with 10 Gm. of sodium salicylate daily and are of no practical significance as far as toxic reactions are concerned. Severe toxic reactions

are marked by hyperpnea, tetany with carpopedal spasm, and progression to maniacal delirium and loss of consciousness. They present a serious situation in the advanced state. Pustular acne is not uncommon with the toxic reaction and is frequently troublesome. It promptly subsides on stopping the drug. The serious toxic reactions in our experience are always preceded by hyperpnea. In this stage reduction of the dose of salicylate or the use of sodium bicarbonate soon relieves the symptoms by reducing the plasma level of the drug. If the drug is continued in the same dosage without sodium bicarbonate, hyperpnea increases and delirium appears. In this stage the use of intravenous saline is necessary to return the body chemistry to normal and relieve the symptoms. We¹⁷ have shown that the chemical changes consist of a respiratory alkalosis with resultant water retention and diminished renal function. It is essential that the premonitory symptoms of severe toxic reactions be well known by those using these large doses of salicylates. In our series of young adults, 20 to 25 grains of sodium salicylate every four hours (six times daily) were usually sufficient to maintain plasma levels of 35 to 50 mg. per 100 cubic centimeters. No sodium bicarbonate was given with this dose and toxic reactions were rarely experienced.

The use of intravenous salicylate is open to considerable question. We were able to maintain more satisfactory plasma levels with oral administration. P. K. Smith¹⁰ has shown that with oral administration the plasma level reaches a peak in one hour. It would appear that intravenous therapy is not necessary. In those patients with heart failure or impending failure, the use of intravenous saline may well be dangerous and may increase the degree of failure. None of our patients receiving intravenous therapy was in cardiac failure and there were no serious reactions. However, nausea and vomiting are very common with intravenous salicylate and in some cases we were forced to discontinue this method of administration because of constant vomiting. After a few hours these patients were able to resume salicylate therapy in large oral doses without difficulty. In our experience intravenous therapy offers no advantage over oral therapy in the control of these patients.

In our group of young adults, the administration of large doses of sodium salicylate was more efficacious than small doses: first, in reducing the febrile response; and, second, in the treatment of acute pericarditis. It did not diminish the period of rheumatic activity as shown by the effect on the sedimentation rate; it did not prevent the occurrence of valvular heart disease; and it did not prevent the progression of polycyclic attacks of rheumatic fever. There may be certain advantages in using large amounts especially at the start of therapy and until the fever and the symptoms have subsided. There seems to be some question as to the necessity for continuing the salicylate after these effects have been achieved. Patients taking large doses have almost constant tinnitus and diminished hearing so that cessation of the drug will make them more comfortable.

It would appear that the use of large amounts of salicylate offers some advantage in the treatment of rheumatic fever. The early reduction of fever and pain would tend to decrease the heart rate and reduce cardiac work. How-

ever, it will not prevent cardiac damage as is shown by the experience of McEachern,⁷ Keith and Ross,¹¹ and ourselves. Moreover, as Swift³ has pointed out, if in attaining this early relief of symptoms the patient is led to believe he is cured and is allowed to resume normal activity, he may suffer as much or more permanent injury than if he were untreated. It is important to emphasize that sodium salicylate in these doses does not bring about a cure. There is still no chemotherapeutic routine which will obviate the need for prolonged reduction in physical activity as the most important method of treatment in acute rheumatic fever.

CONCLUSIONS

1. The use of sodium salicylate in amounts of 10 to 16 Gm. per day will reduce the temperature more quickly in acute rheumatic fever than will small doses. Likewise large doses appear to offer an advantage in the treatment of acute rheumatic pericarditis.

2. The use of sodium salicylate in doses of 10 to 16 Gm. per day will not prevent the development of cardiac damage or the progression of pre-existing heart disease. Large doses of salicylate will not serve to shorten the period of rheumatic activity anymore than small amounts. Large doses of salicylate will not prevent the development of polycyclic attacks of rheumatic fever.

3. The routine use of sodium salicylate by intravenous infusion is not warranted by the evidence presented to obtain a rapid elevation of the plasma salicylate level, to maintain a high plasma level, or to effect the fever or sedimentation rate.

4. If large amounts of salicylate are given, either orally or intravenously, the premonitory signs of toxicity must be recognized early and the dose must be reduced to prevent progression of the symptoms.

5. It appears that the use of large amounts of salicylate may offer some advantage in the first weeks of therapy and may bring about a rapid reduction of the fever and alleviation of the symptoms; but the continued administration of large amounts of this drug until the sedimentation rate is normal is of questionable value.

REFERENCES

1. Miller, J. L.: The Specific Action of Salicylates in Articular Rheumatism, *J. A. M. A.* **63**: 1107-1109, 1914.
2. Hanzlik, P. J., Scott, R. W., and Gauchat, P. C.: The Salicylates. X. The Specificity of Salicylate in Rheumatic Fever, *J. Lab. & Clin. Med.* **4**: 112-122, 1918.
3. Swift, H. F.: Rheumatic Fever, *Am. J. M. Sc.* **170**: 631-647, 1925.
4. Graef, I., Parent, S., Zitron, W., and Wyckoff, J.: Studies in Rheumatic Fever. I. The Natural Course of Acute Manifestations of Rheumatic Fever Uninfluenced by Specific Therapy, *Am. J. M. Sc.* **185**: 197-210, 1933.
5. Coburn, A. F.: Salicylate Therapy in Rheumatic Fever, *Bull. Johns Hopkins Hosp.* **73**: 435-464, 1943.
6. Hanzlik, P. J.: Actions and Uses of Salicylates and Cinchopen in Medicine, *Medicine* **5**: 197-374, 1926.
7. McEachern, G. C.: Use of Oral and Intravenous Salicylate in Acute Rheumatic Fever, *News Letter, AAF Rheumatic Fever Control Program* **2**: 1-8, 1945. Published by Josiah Macy, Jr., Foundation, New York, N. Y.
8. Taran, L. M., and Jacobs, M. H.: Salicylate Therapy in Rheumatic Fever in Children, *J. Pediat.* **27**: 59-68, 1945.

9. Goodman, L., and Gilman, A.: *The Pharmacological Basis of Therapeutics*, New York, 1941, The Macmillan Co., p. 231.
10. Smith, P. K.: Salicylate Metabolism in Normal Subject, *News Letter, AAF Rheumatic Fever Control Program* 2: 8-11, 1945. Published by Josiah Macy, Jr. Foundation, New York, N. Y.
11. Keith, J. D., and Ross, A.: Observations on Salicylate Therapy in Rheumatic Fever, *Canad. M. A. J.* 52: 554-559, 1945.
12. Murphy, G. E.: Salicylate and Rheumatic Activity, *Bull. Johns Hopkins Hosp.* 77: 1-42, 1945.
13. Jones, T. D.: The Diagnosis of Rheumatic Fever, *J. A. M. A.* 126: 481-484, 1944.
14. Ernestene, A. C.: Erythrocyte Sedimentation, Plasma Fibrinogen and Leucocytosis as Indices of Rheumatic Infection, *Am. J. M. Sc.* 180: 12-24, 1930.
15. Levine, S. A.: *Clinical Heart Disease*, ed. 2, Philadelphia, 1942, W. B. Saunders Co., p. 272.
16. Wyckoff, J., DeGraff, A. C., and Parent, S.: The Relationship of Auriculo-Ventricular Conduction Time in Rheumatic Fever to Salicylate Therapy, *AM. HEART J.* 5: 568-574, 1930.
17. Coombs, F. S., Warren, H. A., and Higley, C. S.: Toxicity of Salicylates, *J. Lab. & Clin. Med.* 30: 378-379, 1945.

A REFRACTORY CASE OF SUBACUTE BACTERIAL ENDOCARDITIS DUE TO VEILLONELLA GAZOGENES CLINICALLY ARRESTED BY A COMBINATION OF PENICILLIN, SODIUM PARA- AMINOHIPPURATE, AND HEPARIN

LEO LOEWE, M.D., PHILIP ROSENBLATT, M.D., AND ERNA ALTURE-
WERBER, PH.D., BROOKLYN, N. Y.

SINCE the value of penicillin alone or with heparin has been established,¹⁻⁴ bacterial endocarditis is being studied very intensively. It is not surprising, therefore, that infecting organisms of a bizarre nature are occasionally encountered. A most unique example of a bizarre infecting organism was found in a patient who was admitted to the Jewish Hospital of Brooklyn on April 14, 1944. Before the patient entered our hospital, the organism had been recovered from the blood stream with great difficulty, under the direction of Dr. Gregory Schwartzman, and identified by him and his group as a *Veillonella* species. This same gram-negative anaerobic coccus was isolated by us repeatedly and its biologic characteristics, including its response in the test tube to various anti-infective agents, were studied in great detail. It was considered worth while to report this case (1) because of the unusual nature of the infecting organism, its extreme resistance to penicillin presenting an almost insurmountable obstacle to the successful treatment of the patient, and (2) because of the singular measures employed in overcoming all the difficulties encountered and accomplishing clinical arrest of the infection. The case is further noteworthy because of the huge amounts of penicillin* which were employed, a fact which gives further testimony to the nontoxicity of this agent. Finally, it is the first recorded instance, so far as we know, wherein sodium para-aminohippurate† was used as an indispensable enhancing agent in the actual treatment of a patient infected with a refractory organism.

CASE REPORT

S. Z., a 35-year-old white man, was admitted to the Jewish Hospital of Brooklyn on April 14, 1944, with a history of fever of seven months' duration. The patient's illness began on Sept. 4, 1943, with chills, fever, and pain in the right shoulder. At this time a painless, red spot appeared on the big toe of his right foot. He was admitted to another hospital where a course of atabrine was given without effect. One month later he was transferred to a second hospital where

From the Department of Medicine and the Department of Laboratories, Jewish Hospital of Brooklyn.

Aided by a grant from the John L. Smith Research Fund of the Jewish Hospital of Brooklyn.

Received for publication Feb. 13, 1946.

*We are indebted to Mr. John L. Smith of the Chas. Pfizer & Co., Inc., for the generous supplies of a specially prepared solution of penicillin utilized in these studies.

†We are indebted to Sharp and Dohme, Inc., for the liberal supplies of sodium para-aminohippurate and to Dr. Karl H. Beyer of that organization for his advice and cooperation.

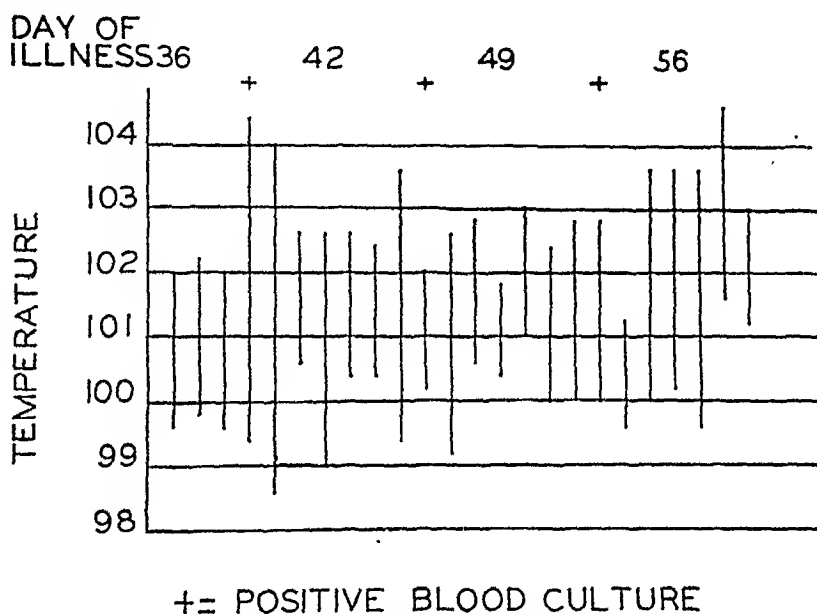
he was treated with massive doses of the sulfonamide drugs. At the latter institution a gram-negative anaerobic organism was isolated from the blood stream which was identified as *Veillonella* species. There was some symptomatic improvement as a result of the chemotherapy, but, as soon as treatment was stopped, the clinical symptoms recurred. The patient denied having had rheumatic fever.

On admission to our institution, the patient was found to be of athletic habitus. His temperature was 100.4° F., pulse rate, 100; respirations, 24; and blood pressure, 105/65. The heart did not appear to be enlarged, but there was a loud, rough, apical systolic murmur. The spleen was slightly tender and palpable 2 fingerbreadths below the costal margin. There were two red spots on the right thumb. Culture of the blood on admission was sterile. The sedimentation rate was 92 mm. in one hour (Westergren method); hemoglobin, 78 per cent; red blood cells, 4,200,000 per milliliter; white blood cells, 7,100 per milliliter, with 70 per cent polymorphonuclear leucocytes, 26 per cent lymphocytes, and 4 per cent monocytes.

Treatment was begun on April 18, 1944, with penicillin and heparin. The patient was given a two-week course of penicillin and heparin by continuous intravenous drip, totalling 3,430,000 units of penicillin and 900 mg. of heparin. Therapy had to be interrupted on one occasion because of violent pyrogenic reactions in which the temperature reached a height of 107° F.

During treatment, the patient ran a daily remittent temperature up to 104° F. which apparently was uninfluenced by the treatment. On May 5 he was given sulfadiazine in dosages up to 9 Gm. daily. This was continued for a period of ten days and was supplemented with 20,000 units of penicillin every two hours intramuscularly during the last four days of this cycle. Again, little or no success attended this treatment except for the fact that the temperature continued at a slightly lower level. Sulfonamides were therefore discontinued, and the patient was again put on continuous intravenous penicillin therapy receiving 240,000 units daily for six days with no clinical benefit. Penicillin was discontinued on May 19, 1944, and oral sulfadiazine was again resumed. On May 24, the oral chemotherapy was supplemented with intravenously administered sulfadiazine; 20 Gm. of the sodium salt, combined with 30 Gm. of urea, in 1,000 ml. of normal saline was administered daily. This was continued until May 31 and was of no benefit to the patient. On June 1, he was again put on continuous intravenous penicillin, receiving 500,000 units daily. This had to be discontinued after four days because of limited supplies. On June 7, massive intravenous sulfadiazine was again started. He received 20 Gm. of the drug combined with 30 Gm. of urea and 1 Gm. of ascorbic acid in 1,000 ml. of normal saline; but because of the mutilated condition of the patient's veins, therapy had to be suspended the following day. The patient received no therapy at all during the next week and the temperature unaccountably declined gradually and reached normal on June 14. On this date, for the first time since admission, culture of the blood yielded a gram-negative anaerobic organism, *Veillonella* species. The organism was thereafter repeatedly recovered from the blood stream until the

infection was apparently arrested. On June 21, the patient was again started on massive cyclic intravenous sulfonamide therapy. He was given 20 Gm. of sulfadiazine plus 30 Gm. of urea and 1 Gm. of ascorbic acid dissolved in 1 liter of distilled water on two successive days each week for the next four weeks. The patient's condition, however, did not improve, and consequently penicillin-heparin was again started on July 14. A fourteen-day course of treatment was given, with daily dosage of one million units of penicillin plus 100 mg. of heparin in 1 liter of solute. Although the temperature curve remained relatively flat during treatment, as soon as it was suspended, the daily, swinging character, with spikes up to 103° F., was resumed (Fig. 1). A blood culture taken during treatment was negative, but one repeated the day treatment was stopped was positive.



+ = POSITIVE BLOOD CULTURE

Fig. 1.—Graph showing typical daily fluctuations in temperature while patient was clinically and bacteriologically active.

The patient's veins were in such poor condition that it was necessary to defer penicillin therapy until August 9, when it was again administered under the same dosage plan. Treatment was continued for nine days, when available veins gave out. During this span of treatment the temperature continued its remittent course, but the daily peaks were on a lower level, i.e., up to 101° F.

In view of the ineffectiveness of treatment up to this point, all therapy was now interrupted and the patient was investigated for possible extracardiac foci of infection. Several devitalized teeth were found and these were surgically removed on Sept. 19, 1944. The patient withstood the procedure well, but his clinical course indicated continued bacterial activity. A blood culture taken on September 25 was again positive.

Up to this date, the patient had been in the hospital for about five and one-half months and had received a total of almost 31 million units of penicillin. Although the endocarditis remained active, his general status was surprisingly good. It was felt that, if nothing else, treatment had succeeded in maintaining a status quo and that, ultimately, persistence and revised dosage schedules would meet with success.

Between September 25 and October 30 the patient was given another course of penicillin. The basic dosage plan was now 2 million units daily. During portions of this course the diluent used was 1,000 ml. of sodium para-aminohippurate in 4 to 8 per cent concentration. Treatment under this plan was entirely probatory and had to be interrupted on several occasions because of complicating local thrombophlebitic reactions. In all, he received 45 million units of penicillin, but, at the end of this span, the temperature curve reflected clinical activity although blood cultures were sterile.

On November 6, an eighteen-day course of treatment was begun. The treatment plan at this time called for 2 million units of penicillin daily dissolved in 1,000 ml. of 4 per cent sodium para-aminohippuric acid. When treatment was discontinued on November 24, there had been absolutely no change in the temperature curve. A blood culture taken on November 28 was positive. About the most that could be said at this juncture was that there still had been no deterioration in the patient's general condition.

Obviously, with so much intravenous work having been done, the patient's veins were seriously compromised. It was therefore necessary to defer further therapy until December 11. At this time the daily dosage plan for penicillin was revised to 5 million units, and, in order to conserve the veins, it was dissolved in 500 ml. normal saline and given by continuous intramuscular drip. Treatment by this route proved extremely painful and distressing and had to be suspended four days later, after a total of 20 million units had been administered.

Continuous intravenous medication was again resumed on December 19; the daily dosage plan at this time varied from 2 to 5 million units of penicillin plus 200 mg. of heparin dissolved in 1,000 ml. of normal saline. At times, the diluent used was 8 per cent sodium para-aminohippurate so that blood assays for penicillin with and without the supplemental use of this drug could be done. Treatment was continued for thirty-one days and was stopped on Jan. 19, 1945; a total of 131 million units of penicillin had been given. During much of this course, the temperature receded and remained flat. This was most encouraging in view of the fact that blood cultures were also negative. However, on January 24, the patient had a chill and the temperature again began its daily remittent course with peaks up to 103° F.

As a result of the encouraging response observed during the previous span of treatment, another course was projected with increasing dosage of penicillin up to 10 million units daily, combined with heparin. The basal daily dosage for a good portion of this period was 5 million units. Treatment was begun on January 31, and continued for thirty-seven days, ending on March 8, 1945; a total of 173 million units of penicillin were given. The general condition of the patient remained in statu quo during this treatment. The temperature curve became irregularly lower and the cycle was finally interrupted because of the apparent futility of the treatment program and the fact that the patient's veins again were badly mutilated.

Probationary in vitro tests had indicated the effectiveness of streptomycin. Pending the acquisition of adequate amounts of this antibiotic and in order to

allow both the patient's morale and his veins to recover, he was sent home and given a respite from hospital routine.

Up to this time, the patient had been in the hospital almost a full year and had received a total of about 467 million units of penicillin. Despite the fact that his endocarditis was clinically and bacteriologically still active, his general condition was quite favorable. There had been no embolic complications.

During the month the patient was at home the organism was again subjected to intensive study. It was finally identified as *Veillonella gazogenes*. Inasmuch as there was unexpected delay in obtaining streptomycin, the organism was retested against penicillin. In vitro tests showed bacteriostasis at 10 units of penicillin per milliliter. However, 30 units of penicillin per milliliter were required for a complete bactericidal effect. It was apparent that the previous dosage schedules had been inadequate, since blood assays had never reached appropriate therapeutic levels. Since our studies⁵ had shown that we could expect serum penicillin levels of approximately 1 unit per milliliter for each million units of penicillin administered daily, it was obvious that the requisite dosage schedule called for at least 30 million units per day. While it was theoretically possible to administer this huge daily dosage of penicillin it was felt that further experimentation with the use of para-aminohippuric acid as an enhancing agent was indicated. These experiments (Tables I and II) were accordingly carried out during the first few weeks following the patient's readmission to the hospital on April 9, 1945.

On his return to the hospital, it was evident that the patient's general condition had not deteriorated. He was febrile and two blood cultures taken on April 5 (at home) and April 10 revealed numerous colonies of *Veillonella gazogenes*. Probatory experiments with various dosage schedules of penicillin together with para-aminohippuric acid (Table II) led us to assume that adequate therapeutic levels could be consistently maintained if the following program was followed: (1) minimum daily dosages of 10 million units of penicillin, (2) minimum daily dosage of 240 Gm. of sodium para-aminohippurate.

The patient was accordingly started on his new treatment program on May 11, 1945. He was given, daily, 10 million units of penicillin dissolved in 2 liters of 12 per cent sodium para-aminohippuric acid solution to which were added 50 mg. of heparin. This modest amount of heparin, by preventing regional thrombophlebitis, has been found effective generally in the face of huge penicillin dosage. Over a period of sixteen days (Figs. 2 and 3), he received the equivalent of thirteen full days of treatment, or 130 million units of penicillin. The results were prompt and dramatic. Within three days after the program was initiated, the temperature became normal and has remained so far almost six months. As a prophylactic measure, the remainder of his potentially infected teeth were surgically removed. The patient was discharged from the hospital on June 23, 1945, clinically well.

At the time of discharge the patient weighed 190 pounds (86 kg.) as contrasted with a low of 166 pounds (75 kg.) on April 10, 1945. The spleen, which had previously been consistently palpable, receded promptly. The sedimentation rate

was 12 mm. in one hour as compared with a high of 95 mm. on May 5, 1944. The blood picture showed hemoglobin, 90 per cent; red blood cells, 4,660,000; white blood cells, 6,850, with a differential of 55 per cent polymorphonuclear

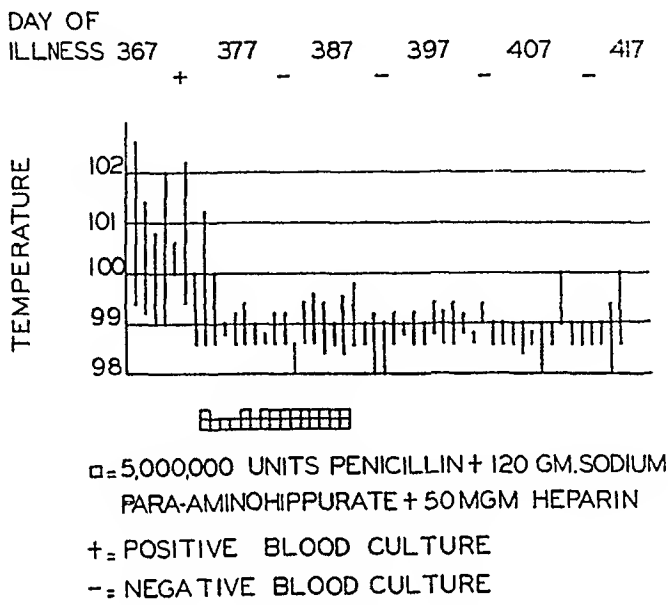


Fig. 2.—Graph showing response of patient to curative cycle of therapy.

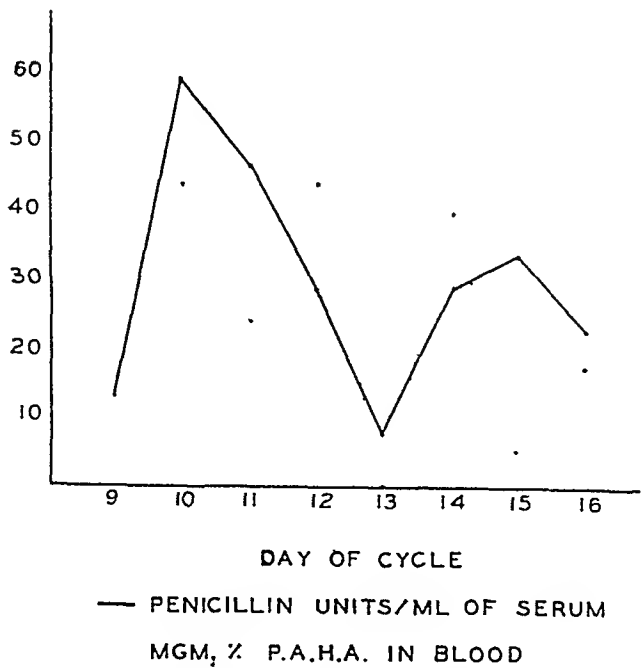


Fig. 3.—Graph showing actual blood assays of penicillin and para-aminohippuric acid during curative cycle of therapy.

leucocytes, 44 per cent lymphocytes, and 1 per cent eosinophiles. Previously, there had been a peristent secondary anemia which was controlled only by repeated transfusions of whole blood. The albumin and erythrocytes found in

the urine during the active phases of the disease disappeared with termination of the infection. The patient has been seen at intervals since his discharge. His condition is excellent, and cultures of the blood have been consistently sterile.

EXPERIMENTAL STUDIES

Blood cultures were taken in 0.1 per cent brain-heart infusion agar broth (Difco) and 0.1 per cent Savita glucose agar broth, to both of which was added 0.1 per cent agar. The cultures were incubated for four to seven days at 37° C. and then surface plated on blood agar by inoculating the plates with the incubated blood broth culture. The transplanted cultures were placed in a candle jar (10 per cent carbon dioxide) and kept for three days at 37° C. Colonies were picked from these plates, transferred, and identified. After repeated transfers, the use of a candle jar could be dispensed with and the organism could be grown sluggishly at room temperature. The organism was identified as *Veillonella gazogenes*, which, according to Bergey,⁶ is prevalent in the saliva of man and other animals. Although it was not possible to isolate the organism from the patient's mouth or from his tooth sockets and roots, the portal of entry may nevertheless well have been the oral cavity.

As indicated in the clinical review, the organism was extremely resistant to daily dosages of penicillin per se up to and including 10 million units. In vitro titrations of suspensions of the organism against varying concentrations of penicillin showed bacteriostasis at 10 units of penicillin per milliliter. A complete bactericidal effect was not obtained until the concentration of 30 units of penicillin per milliliter was reached. Although streptomycin was not available for clinical use, it was possible to obtain some for in vitro experimental purposes. It was found that the inhibiting concentration of streptomycin was 10 units per milliliter.

It was necessary to evaluate dosage schedules of the chemotherapeutic agents in the light of these facts. Previous studies⁵ had indicated that with a given dosage schedule of penicillin administered by the continuous intravenous route, expected sustained serum assays approached 0.1 unit per 100,000 units daily. In other words, in order to attain bactericidal serum penicillin levels in this patient, the daily dosage theoretically would have had to be at least 30 million units.

Because variations in blood levels exist in the individual case, an experiment was designed to see what levels could be obtained in this patient with varying dosages of penicillin. Equivalent dosages of penicillin were calculated and dissolved in 166 ml. of normal saline to cover an experimental period of two hours for each dose. The patient was carefully observed throughout so that the prescribed amounts of penicillin were infused. Blood was drawn at the end of each hour and serum penicillin assays were performed according to the method of Rosenblatt, Altire-Werber, Kashdan, and Loewe.⁷ Table I indicates the serum penicillin levels obtained with equivalent daily dosages up to 30 million units per day.

TABLE I. SERUM PENICILLIN LEVELS WITH VARYING DOSAGE OF PENICILLIN

PENICILLIN* UNITS/HR. ($\times 1,000$)	EQUIVALENT DAILY DOSAGE ($\times 1,000$)	SERUM PENICILLIN UNITS/ML.				
		1 HOUR	2 HOURS	AVERAGE	THEORETICAL†	DEVIATION
415	9,960	3.33	12.0	7.67	9.96	-2.29
457.5	10,980	8.57	8.57	8.57	10.98	-2.41
500	12,000	15.0	12.0	13.5	12.0	+1.5
541.5	12,960	15.0	15.0	15.0	12.9	+2.1
582.5	13,980	7.5	15.0	11.25	13.98	-2.74
625	15,000	15.0	15.0	15.0	15.0	0.0
667.5	16,020	24.0	15.0	19.5	16.0	+3.5
						Total -7.44
						+7.1
710	17,040	20.0	20.0	20.0	17.0	+3.0
750	18,000	12.0	15.0	13.5	18.0	-4.5
792.5	19,020	15.0	30.0	22.5	19.0	+3.5
835	20,040	30.0	24.0	27.0	20.0	+7.0
875	21,000	15.0	30.0	22.5	21.0	+1.5
918	22,020	30.0	30.0	30.0	22.0	+8.0
960	23,010	30.0	30.0	30.0	23.0	+7.0
1,000	24,000	17.1	20.0	18.56	24.0	-5.44
1,042.5	25,020	24.0	30.0	27.0	25.0	-2.0
1,085	26,040	30.0	40.0	35.0	26.0	+9.0
1,127.5	27,060	30.0		30.0	27.0	+3.0
1,170	28,080	15.0	20.0	17.5	28.0	-9.5
1,210	29,100	48.0	40.0	44.0	29.1	+14.9
1,260	30,220	60.0	40.0	50.0	30.2	+10.8
						Total -21.44
						+67.7

*Diluent was 83 ml. of normal saline per hour. This is equivalent to approximately 1,000 ml. per day.

†This is based upon expected serum penicillin level of 0.1 unit per daily dosage of 100,000 units.

It is seen that with dosages up to 15 million units per day the actual figures obtained were fairly close to theoretically expected values. With dosages above 15 million units daily, most of the actual serum assays tended to be higher than the theoretical. This may possibly be due to the fact that the point of maximal renal clearance for penicillin had been exceeded. This problem, however, is being further investigated.

According to this study, daily dosage of 20 million units of penicillin or more might consistently yield the requisite bactericidal level of 30 units per milliliter of serum. It was felt that a saving of penicillin could be effected through the concurrent use of sodium para-aminohippurate, which Beyer and his co-workers⁸ had proposed as an agent for aiding the economy with which the body utilizes penicillin.

Our previously published studies⁹ confirmed Beyer's observations, but it was found necessary to administer at least 200 Gm. of sodium para-aminohippurate daily in order to attain blood concentrations sufficient to augment serum penicillin levels appreciably. In order to administer this amount of the

TABLE II. AUGMENTATION OF SERUM PENICILLIN LEVELS BY SIMULTANEOUS ADMINISTRATION OF PARA-AMINOHIPPURIC ACID

HR.	PENICILLIN* UNITS/HR.	EQUIVALENT DAILY DOSAGE	SODIUM PARA-AMINOHIPPURATE†	BLOOD SERUM PENICILLIN UNITS/ML.	ASSAY P. A. H.‡ MG. %
1	417,500	10,020,000	0	7.5	—
2			0	7.5	—
3			{12 per cent Sodium P.A.H. and priming doses of 50 c.c. 20 per cent solution at three and five hours	15.0	39.7
4				15.0	27.6
5				15.0	59.6
6				15.0	47.5
7			0	15.0	24.2
8			0	15.0	10.2
1	625,000	15,000,000	0	12.0	—
2			0	13.2	—
3			{12 per cent Sodium P.A.H. and priming doses of 50 c.c. 20 per cent solution at three and five hours	20.0	34.1
4				30.0	35.0
5				30.0	51.8
6				30.0	60.5
7			0	30.0	26.6
8			0	30.0	12.3
1	832,500	19,980,000	0	15.0	—
2			0	15.0	—
3			{12 per cent Sodium P.A.H. and priming doses of 50 c.c. 20 per cent solution at three and five hours	30.0	29.4
4				40.0	32.8
5				40.0	61.3
6				48.0	60.5
7			0	48.0	31.5
8			0	40.0	12.9

*During control run of two hours (see text), the diluent for penicillin was 166 ml. of normal saline. This is equivalent to a daily intravenous of approximately 2,000 milliliters.

†During sodium para-aminohippurate run of four hours the diluent for penicillin was 333 ml. of 12 per cent sodium para-aminohippurate in distilled water. This is equivalent to 2 liters daily, or 240 Gm. of the drug. The actual amount given during the four-hour period was 48 grams.

‡P. A. H.=Sodium para-aminohippurate.

enhancing agent effectually, the total daily volume of fluid given intravenously had to be increased from 1 to 2 liters, since a 20 per cent concentration of sodium para-aminohippurate was found to be too irritating for continuous venoclysis. A 12 per cent concentration of the drug (120 Gm. per liter) was satisfactory for maintenance purposes.

Table II summarizes an experiment designed to test the enhancing effect of para-aminohippuric acid. Study of the table shows consistent augmentation of the serum penicillin levels by the simultaneous administration of sodium para-aminohippurate. Although the short-term experiment indicated that a minimum daily dosage of 15 million units of penicillin together with para-aminohippurate might be required for optimum results, it was felt that under actual clinical conditions, there might be a cumulative effect of the antibiotic with smaller dosage. It was decided, therefore, that the projected therapeutic course should encompass the simultaneous, continuous administration of 10 million units of penicillin daily dissolved in 2 liters of 12 per cent sodium para-aminohippurate in distilled water. Heparin was added in order to maintain a continuous intravenous flow and make possible an uninterrupted span of treatment.

Fig. 3 indicates the actual serum penicillin and para-aminohippuric acid levels obtained during this span of treatment. The determinations were taken usually at the end of a day's run, prior to attaching a fresh bottle of soluton. It is observed that most of the penicillin levels are within or above the desired effective therapeutic zone. The fact that this course of treatment resulted in the apparent clinical arrest of the disease process is confirmation of the validity of the experimental approach.

As a corollary to what has been presented, it was necessary to ascertain the effect, if any, of sodium para-aminohippurate upon the infecting organism. Titrations were therefore carried out in brain-heart infusion broth, and the results are summarized in Table III.

TABLE III. TABLE SHOWING RESISTANCE OF VEILLONELLA GAZOGENES TO THERAPEUTIC AGENTS

DRUG	BACTERIOSTASIS	MINIMUM LETHAL DOSE
Penicillin.....	10 Oxford units per milliliter	30 Oxford units per milliliter
Penicillin plus P. A. H.,* 20 mg.%..	10 Oxford units per milliliter	30 Oxford units per milliliter
Penicillin plus P. A. H., 30 mg.%..	10 Oxford units per milliliter	26 Oxford units per milliliter
Penicillin plus P. A. H., 40 mg.%..	10 Oxford units per milliliter	20 Oxford units per milliliter
Penicillin plus P. A. H., 50 mg.%..	10 Oxford units per milliliter	15 Oxford units per milliliter
P. A. H.....	40 mg. per cent	163 mg. per cent
P. A. H. plus penicillin, 10 units/ml.	16 mg. per cent	63 mg. per cent
Streptomycin.....	10 units per milliliter	10 units per milliliter

*P. A. H.=Sodium para-aminohippurate.

It was noted that sodium para-aminohippurate itself is bacteriostatic at a concentration of 40 mg. per cent and bactericidal at 160 mg. per cent. With a standard level of 10 units of penicillin per milliliter in brain-heart infusion broth, a synergistic effect was observed when varying concentrations of sodium para-aminohippurate were added. The bacteriostatic and minimal lethal zones of sodium para-aminohippurate were reduced to 16 mg. per cent and 63 mg. per cent, respectively, in the presence of 10 units of penicillin per milliliter of test broth.

The converse of what has been discussed is also summarized in Table III. To brain-heart infusion broth containing 20 to 50 mg. per cent of sodium para-aminohippurate were added varying concentrations of penicillin. These were inoculated with *Veillonella gazogenes* and incubated for twenty-four hours. At a concentration of 50 mg. per cent of sodium para-aminohippurate the bacteriostatic level of penicillin remained at 10 units per milliliter in all instances, but the bactericidal zone was progressively reduced until it reached 15 units of penicillin per milliliter, almost approximating the bacteriostatic level.

These experiments indicate a pronounced synergistic effect between penicillin and sodium para-aminohippurate. Thus, consistent minimal lethal levels against the infecting organism in this case could obviously be reached more readily with the conjoint use of both drugs than could have been achieved by the use of either one, per se.

SUMMARY AND CONCLUSIONS

1. A unique case of subacute bacterial endocarditis due to *Veillonella gazogenes* has been presented.

2. Massive sulfonamide therapy was ineffectual in terminating the infection.

3. Twelve courses of penicillin therapy of varying length, combined at times with adjuvants such as sulfonamides and heparin, failed to sterilize the blood stream although progress of the infection was retarded during the year of this treatment. Dosages of penicillin up to 10 million units per day by the continuous intravenous route were nontoxic and well tolerated. A total of 466,670,000 units of penicillin was used during this period.

4. In vitro studies revealed bacteriostasis for the organism at 10 units per milliliter of streptomycin and penicillin. The minimum lethal dose was 10 units per milliliter and 30 units per milliliter for streptomycin and penicillin, respectively.

5. With a constant concentration of 10 units per milliliter of penicillin, the bacteriostatic and minimum lethal dose of sodium para-aminohippurate was 16 mg. per cent and 63 mg. per cent, respectively. This contrasts with bacteriostatic and lethal doses of 40 mg. per cent and 163 mg. per cent, respectively, of sodium para-aminohippurate, per se.

6. With concentrations of sodium para-aminohippurate varying from 20 to 50 mg. per cent, the minimum lethal dose of penicillin against the infecting organism was lowered as much as 15 units per milliliter.

7. These data were clinically applied with satisfactory results by the simultaneous daily intravenous administration of penicillin and sodium para-aminohippurate in doses of 10 million units and 240 Gm., respectively, over a period of sixteen days. Heparin was also incorporated for its beneficial effect in maintaining an uninterrupted venoclysis.

8. This is the first case in which sodium para-aminohippurate has been used with penicillin in the actual clinical arrest of an infection otherwise highly resistant to the action of penicillin alone.

9. The case demonstrates the need for close collaboration between the laboratory and the clinician for optimum results.

The authors desire to express their appreciation of the contributions made by Miss M. Kozak, Mr. M. Russell, and Miss F. Kashdan.

REFERENCES

1. Loewe, L., Rosenblatt, P., Greene, H. J., and Russell, M.: Combined Penicillin and Heparin Therapy of Subacute Bacterial Endocarditis, Report of Seven Consecutive Successfully Treated Patients, J. A. M. A. 124: 144-149, 1944.
2. Loewe, L.: The Combined Use of Penicillin and Heparin in the Treatment of Subacute Bacterial Endocarditis, Canad. M. A. J. 52: 1-14, 1945.
3. Loewe, L.: The Combined Use of Anti-Infectives and Anti-Coagulants in the Treatment of Subacute Bacterial Endocarditis, Bull. New York Acad. Med. 21: 59-86, 1945.

4. Conference on Therapy, Cornell University Medical College and the New York Hospital, Departments of Pharmacology and Medicine, The Treatment of Subacute Bacterial Endocarditis, Jan. 11, 1945, New York State J. Med. 45: 1452-1459, 1945.
5. Loewe, L., Rosenblatt, P., Russell, M., and Altire-Werber, E.: The Superiority of the Continuous Intravenous Drip for the Maintenance of Effectual Serum Levels of Penicillin: Comparative Studies With Particular Reference to Fractional and Continuous Intramuscular Administration, J. Lab. & Clin. Med. 30: 730-735, 1945.
6. Bergey, D. H., Breed, R. S., Murray, E. G. D., and Parker Hitchens, A.: Bergey's Manual of Determinative Bacteriology, Baltimore, 1939, Williams and Wilkins Co., pp. 287-288.
7. Rosenblatt, P., Altire-Werber, E., Kashdan, F., and Loewe, L.: A Method for the Administration of Penicillin in Body Fluids, J. Bact. 48: 599, 1944.
8. Beyer, K. H., Flippin, H., Verwey, W. F., and Woodward, R.: The Effect of Para-Aminohippuric Acid on the Plasma Concentration of Penicillin in Man, J. A. M. A. 126: 1007-1009, 1944.
9. Loewe, L., Rosenblatt, P., Altire-Werber, E., and Kozak, M.: The Prolonging Action of Penicillin by Para-Aminohippuric Acid, Proc. Soc. Exper. Biol. & Med. 58: 298-300, 1945.

CARDIAC OUTPUT IN HEART FAILURE

J. R. E. SUÁREZ, M.D., J. C. FASCILOLO, M.D., AND A. C. TAQUINI, M.D.
BUENOS AIRES, ARGENTINA

SINCE the pioneer work of von Plesch in 1909,¹ extensive research has been done on the behavior of cardiac output in valvular, hypertensive, and coronary heart diseases. Von Plesch, like most of his followers,²⁻⁴⁵ found great variability in the cardiac output of cardiac patients with or without failure. Their results are likely to be criticized because of the methods used or because basal conditions were not accurately observed. In general, however, their results showed normal or diminished cardiac output.

Starr and his associates,⁴⁶⁻⁴⁸ using the ethyl iodide method modified by Starr and Gamble,⁴⁹ observed that generally the cardiac output was normal in compensated cardiac patients. In patients with failure they usually found a diminished cardiac output, though in some the values were within normal range. They failed to find a correlation between cardiac output and functional capacity of the heart. Altschule and Blumgart,⁵⁰ using the same method as Starr and his associates, observed that the cardiac output was at the lower limit of normal in a patient with mitral, tricuspid, and aortic stenosis and insufficiency.

Grollman and his co-workers⁵¹ investigated the possible application of the acetylene technique in cardiac patients, showing that it was desirable to take at least three samples during the rebreathing period. In their small series of patients with severe heart failure, the cardiac output was diminished in some and within the normal range in others. Using the same method, McMichael⁵² showed that the cardiac output was normal in compensated cardiac patients and diminished in those with failure, but no consistent correlation could be demonstrated between the degree of the insufficiency and the cardiac output. Taquini and his co-workers,⁵³ using the acetylene technique with three or four samples, studied a series of patients with mitral stenosis, either compensated or with a mild degree of failure. In their cases the figures for the average cardiac index were lower than those for the normal controls, both in patients with normal sinus rhythm and in those with auricular fibrillation.

Some investigators were especially interested in finding a correlation between the severity of heart failure and cardiac output. Harrison and his associates⁵⁴ and Harrison,⁵⁵ using the acetylene method (three or four samples), found that in general the cardiac output was diminished in patients with cardiac failure. They concluded, however, that there was no relation between the degree of the

Center of Cardiologic Research, Virginio F. Grego Foundation. Faculty of Medicine, University of Buenos Aires, Buenos Aires, Argentina.
Received for publication Dec. 22, 1945.

insufficiency and the cardiac output or the arteriovenous oxygen difference. In support of this conclusion they pointed out that, in the same patient, a clinical improvement can be associated with increased, diminished, or no change in cardiac output and arteriovenous oxygen difference.

McGuire, Hauenstein, and Shore,⁵⁶ using the acetylene and the direct Fick method on a small number of patients, could not find a consistent correlation between the degree of heart failure and the diminution of cardiac output. Later,⁵⁷⁻⁵⁹ using the three-sample acetylene method on a greater number of cases of congestive heart failure, they observed that, as the insufficiency was more severe, the cardiac index was reduced further, with only a few exceptions which could be readily explained on the basis of such extracardiac factors as metabolism, venous pressure, hyperpnea, and so forth. They divided the patients into four groups according to the severity of the congestive heart failure, noting that the difference in cardiac index of any two consecutive groups was not statistically significant although it was significant between the first and the last group.

Stewart and co-workers^{60, 61} pointed out that a close correlation could be drawn between the clinical condition and the cardiac output in rheumatic, hypertensive, arteriosclerotic, and syphilitic heart disease. Using the three-sample acetylene method, they showed that the average cardiac index was slightly reduced in patients who never had experienced cardiac insufficiency, and that it was much lower in cases with congestive heart failure. In a group of patients studied after recovery from failure, the figures for the average cardiac index showed a value between those of the patients with compensated heart disease and those of the patients with congestive failure. The clinical improvement was accompanied by an increase of the cardiac output although the values of the first group were not reached. These results led Stewart and his co-workers to the conclusion that there is an inverse correlation between the degree of heart failure and the cardiac index.

Stewart and his co-workers⁶⁰ found that "single lesions are not incompatible with a fairly normal circulation at rest, but in all instances in which there is more than one lesion functional alterations appear." They held also that aortic stenosis combined with other valvular lesions resulted in marked decrease in function. On the other hand, aortic regurgitation seemed to be of functional benefit when superimposed on mitral stenosis and insufficiency and resulted in less impairment of the circulation than was found in mitral stenosis and insufficiency alone. The same authors said, "The order of magnitude of the functional defect increased progressively in going from the mitral stenosis and insufficiency, aortic insufficiency group, to the mitral stenosis and insufficiency group, to the mitral stenosis and insufficiency, aortic stenosis and insufficiency group."

MATERIAL AND METHODS

A total of seventy-five determinations were made in forty-two patients. They were grouped under the following diagnoses:

DIAGNOSIS	NUMBER OF PATIENTS	NUMBER OF DETERMINATIONS
Mitral stenosis and insufficiency, sinus rhythm.....	13	23
Mitral stenosis and insufficiency, auricular fibrillation.....	9	20
Mitral stenosis and insufficiency, aortic insufficiency.....	1	1
Mitral stenosis and insufficiency, tricuspid stenosis and insufficiency.....	2	2
Mitral stenosis, interauricular septal defect.....	3	5
Aortic insufficiency.....	2	3
Aortic stenosis and insufficiency.....	2	5
Hypertensive and coronary heart disease.....	10	16
Total.....	42	75

The patients were classified according to their functional capacity at the moment of the determinations, whether they were being treated or not, following the criteria and nomenclature of the New York Heart Association.⁶³ Our results in a group of seventeen normal subjects were used as controls.

The oxygen consumption was determined by an open circuit method using a Tissot spirometer; the air was collected in ten-minute periods. The arterio-venous oxygen difference was determined with the acetylene method of Grollman⁶²; four samples were taken during the rebreathing period. The gas analyses were carried out in the Haldane apparatus with a device for the absorption of the acetylene, and a 12 c.c. burette was used. All the determinations were carried out under basal conditions with the patient sitting in a comfortable arm-chair at an angle of 105 degrees and with the knees flexed. In every case the patient had been trained to carry out the procedure beforehand.

A statistical evaluation of the results was carried out using the following equations: standard deviation = $\sigma = \sqrt{\frac{\sum d^2}{(n-1)}}$; and standard

error = $\epsilon = \sqrt{\frac{\sum d^2}{n(n-1)}}$. In groups of less than ten cases the following

equations were applied: standard deviation = $\sigma = \sqrt{\frac{\sum d^2}{(n-3)}}$; and standard

error = $\epsilon = \sqrt{\frac{\sum d^2}{n(n-3)}}$. Comparing the different groups, the standard deviation of the difference between the averages was calculated according to the

equation $\sqrt{E_I^2 + E_{II}^2}$. The differences were considered statistically significant when they were equal to or greater than three times their standard deviation and very probably real when they fell between two and three times their standard deviation.

RESULTS

In Tables I to V are summarized the results of all the determinations. The average values in each group with the various lesions follow:

Mitral Stenosis and Insufficiency, Sinus Rhythm.

Cardiac Index: Class I, 2.27 liters per square meter per minute (four patients). Class II, 1.99 (six patients). Class III, 1.79 (four patients).

Arteriovenous Oxygen Difference: Class I, 65.5 c.c. per liter of blood. Class II, 66.3. Class III, 80.1.

Heart Rate: Class I, 68 per minute. Class II, 69. Class III, 88.

Systolic Output per Square Meter: Class I, 34.1 c.e. per square meter of body surface. Class II, 29.0. Class III, 20.4.

Mitral Stenosis and Insufficiency, Auricular Fibrillation.

Cardiac Index: Class II, 1.99 liters per square meter per minute (nine patients). Class III, 1.28 (1 patient).

Arteriovenous Oxygen Difference: Class II, 70.7 c.c. per liter of blood. Class III, 110.6.

Heart Rate: Class II, 72 per minute. Class III, 78.

Systolic Output per Square Meter: Class II, 28.3 c.e. per square meter of body surface. Class III, 16.5.

Mitral Stenosis and Insufficiency, Aortic Insufficiency.

Cardiac Index: Class II, 2.02 liters per square meter per minute (one patient).

Arteriovenous Oxygen Difference: Class II, 65.6 c.c. per liter of blood.

Heart Rate: Class II, 73 per minute.

Systolic Output per Square Meter: Class II, 27.5 c.c. per square meter of body surface.

Mitral Stenosis and Insufficiency, Tricuspid Stenosis and Insufficiency.

Cardiac Index: Class II, 1.95 liters per square meter per minute (one patient). Class IV, 1.56 (one patient).

Arteriovenous Oxygen Difference: Class II, 74.0 c.c. per liter of blood. Class IV, 97.4.

Heart Rate: Class II, 82 per minute. Class IV, 98.

Systolic Output per Square Meter: Class II, 23.7 c.c. per square meter of body surface. Class IV, 15.9.

Mitral Stenosis and Insufficiency, Interauricular Septal Defect.

Cardiac Index: Class II, 2.31 liters per square meter per minute (two patients). Class III, 1.57 (one patient).

Arteriovenous Oxygen Difference: Class II, 59.7 c.c. per liter of blood. Class III, 88.0.

Heart Rate: Class II, 59 per minute. Class III, 70.

Systolic Output per Square Meter: Class II, 39.1 c.e. per square meter of body surface. Class III, 22.2.

Aortic Insufficiency.

Cardiac Index: Class I, 2.94 liters per square meter per minute (one patient). Class III, 2.27 (one patient).

Arteriovenous Oxygen Difference: Class I, 53.3 c.c. per liter of blood. Class III, 68.1.

Heart Rate: Class I, 76 per minute. Class III, 70.

Systolic Output per Square Meter: Class I, 38.8 c.e. per square meter of body surface. Class III, 32.3.

Aortic Stenosis and Insufficiency.

Cardiac Index: Class II, 2.02 liters per square meter per minute (one patient). Class III, 1.68 (one patient).

Arteriovenous Oxygen Difference: Class II, 61.6 c.c. per liter of blood. Class III, 86.8.

Heart Rate: Class II, 74 per minute. Class III, 67.

Systolic Output per Square Meter: Class II, 27.2 c.e. per square meter of body surface.

Hypertensive and Coronary Heart Disease.

Cardiac Index: Class I, 2.66 liters per square meter per minute (one patient). Class II, 2.11 (three patients). Class III, 1.82 (five patients). Class IV, 1.60 (two patients).

Arteriovenous Oxygen Difference: Class I, 49.4 c.c. per liter of blood. Class II, 61.5. Class III, 73.3. Class IV, 88.9.

Heart Rate: Class I, 73 per minute. Class II, 63. Class III, 72. Class IV, 77.

Systolic Output per Square Meter: Class I, 36.4 c.c. per square meter of body surface. Class II, 33.7. Class III, 26.0. Class IV, 21.0.

In the calculation of these results, the various determinations on the same individual were averaged, provided that the functional capacity had not changed. In the few cases in which a change was observed in the functional capacity, the results obtained in each case were considered separately within the corresponding capacity group.

With few exceptions, which will be discussed later, the data show that the average values of the patients with different lesions are similar provided the functional capacity is the same. Fig. 1, where the average cardiac index of the

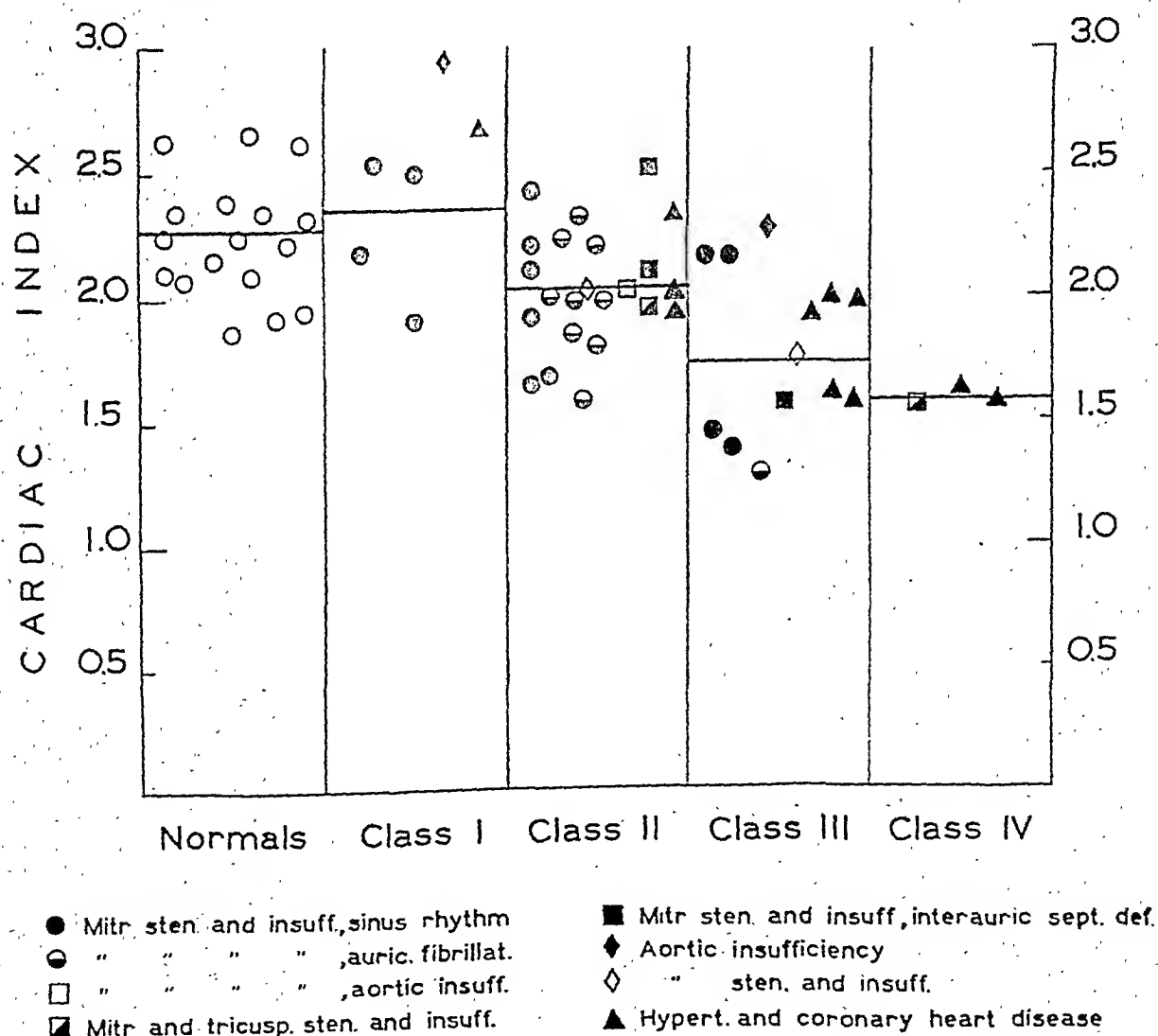


Fig. 1.—Cardiac index of normal patients and those with heart disease. Each symbol represents the average cardiac index of each case. The horizontal lines represent the average cardiac index of all the cases of each group (aortic insufficiency was not included).

TABLE I. MITRAL STENOSIS AND INSUFFICIENCY, SINUS RHYTHM

SUBJECT	SEX	AGE	BODY SUR- FACE	DATE	FUNCTIONAL CAPACITY AND TREATMENT	HEART RATE	OXYGEN CON- SUMPTION	B. M. R.	A-V O ₂ DIFFER- ENCE	CARDIAC OUTPUT	CARDIAC INDEX	SYSTOLIC OUTPUT	SYSTOLIC OUTPUT PER SQ. M.
		YR.	M. ²			PER MIN.	C.C. PER MIN.	%	C.C. PER LITER	LITERS PER MIN.	1/M. ² PER MIN.	C.C.	C.C./M. ²
1	M	24	1.75	30/ 7/42	Class I Without treatment	83	287	+20.0	79.3	3.62	2.07	43	24.5
C. T.				31/ 7/42	Class I Without treatment	82	292	+22.2	73.1	3.99	2.28	48	27.4
2	M	19	1.92	20/11/42	Class I Without treatment	72	245	- 9.9	65.4	3.75	1.95	52	27.0
D. C.				21/11/42	Class I Without treatment	48	252	- 7.3	71.4	3.53	1.84	73	37.8
3	F	31	1.47	1/ 7/43	Class I Without treatment	60	218	+17.5	57.4	3.80	2.58	63	42.8
M. de M.				2/ 7/43	Class I Without treatment	76	208	+12.3	57.0	3.65	2.48	48	32.6
4	M	33	2.00	31/ 7/44	Class I Without treatment	58	291	+ 6.6	58.0	5.02	2.51	85	42.5
M. M.				11/10/44	Class I Without treatment	64	310	+13.6	62.7	4.95	2.47	77	38.5
5	F	36	1.67	20/ 8/41	Class II Without treatment	77	245	+16.4	66.6	3.68	2.20	48	28.7
R. de G.													
6	F	43	1.81	28/ 7/41	Class II Without treatment	68	197	-12.5	66.2	2.97	1.64	43	23.7
M. de O.													
7	F	41	1.51	10/11/42	Class II Without treatment	78	200	+ 5.0	52.6	3.80	2.52	49	32.3
A. de B.				13/11/42	Class II Without treatment	78	191	+ 1.6	54.6	3.50	2.32	45	29.7
8	M	35	1.70	4/ 5/42	Class II On digitalis and quinidine								
J. L.				6/ 5/42	Class II On digitalis and quinidine	62	235	+ 1.2	64.7	3.63	2.13	59	34.5
9	F	38	1.52	23/ 4/42	Class II On digitalis	60	255	+ 9.6	72.2	3.53	2.08	59	34.5
A. de S.				24/ 4/42	Class II On digitalis	68	193	+ 0.8	69.6	2.77	1.82	41	26.8
10	M	24	1.58	12/11/41	Class III Without treatment	62	175	- 8.5	57.2	3.06	2.01	49	32.5
A. C.				27/ 4/42	Class II Off digitalis for three days	74	188	-12.5	82.0	2.30	1.45	33	20.9
11	M	16	1.56	5/ 5/42	Class II Off digitalis for eleven days	60	221	+ 2.5	77.4	2.85	1.80	47	30.1
J. A.				7/ 5/41	Class III Without treatment	70	204	- 5.6	82.3	2.48	1.57	35	22.1
12	F	28	1.69	29/ 7/42	Class III On digitalis	107	250	0	74.0	3.37	2.16	31	19.9
S. de C.													
13	F	54	1.55	8/11/44	Class III Without treatment	100	245	+13.5	66.9	3.66	2.16	37	22.1
M. de V.				10/11/44	Class III Without treatment	70	211	+12.5	96.6	2.18	1.41	31	20.1
						77	210	+12.2	99.3	2.10	1.35	27	17.6

TABLE II. MITRAL STENOSIS AND INSUFFICIENCY, AURICULAR FIBRILLATION

SUBJECT	SEX	AGE		BODY SURFACE		DATE	FUNCTIONAL CAPACITY AND TREATMENT		HEART RATE		OXYGEN CONSUMPTION		B. M. R.		A-V O ₂ DIFFERENCE		CARDIAC OUTPUT		CARDIAC INDEX		SYSTOLIC OUTPUT	
		YR.		M. ²					PER MIN.		C.C. PER MIN.		%		C.C. PER LITER		LITERS PER MIN.		1/M. ² PER MIN.		C.C.	
14 C. V.	F	17		1.65		16/ 4/42 21/ 4/42	Class II Class II	On digitalis On digitalis	85 70	237 216			+ 3.7 - 5.2		77.0 71.0		3.07 3.04		1.86 1.85		36 43	
15 R. C.	M	34		2.05		28/ 4/42 18/ 6/41 23/ 6/41 27/ 6/41	Class II Class II Class II Class II	On digitalis On digitalis On digitalis On digitalis	95 90 90 90	356 335 365 297			+26.8 +26.7 +30.5 + 6.3		82.1 75.0 72.0 74.9		4.33 4.73 5.07 3.96		2.11 2.30 2.47 1.92		48 45 52 56	
16 C. de L.	F	44		2.06 2.05 1.51		5/12/41 15/12/41 10/ 4/42 13/ 4/42 14/ 4/42 8/ 8/41	Class II Class II Class II Class II Class II Class II	Without treatment On digitalis On digitalis On digitalis On digitalis On digitalis	90 72 65 60 62 60	297 270 210 201 196 222			- 3.8 +11.6 + 6.9 + 4.1 - 2.5		78.0 68.3 77.0 57.2		4.86 2.69 2.94 2.55 3.88		2.35 1.78 1.94 1.68 2.32		44 67 41 49 41 65	
17 G. C.	M	25		1.67			Class II	On digitalis	80	250			+ 3.8		62.3		4.01		2.10		50	
18 D. de C.	F	39		1.91		22/ 8/42 27/ 8/42	Class II Class II	On digitalis On digitalis	77	237			- 0.6		66.1		3.58		1.87		46	
19 L. F.	F	33		1.63		14/10/42 15/10/42	Class II Class II	On digitalis On digitalis	68 62	246 233			+19.7 +13.7		68.2 65.5		3.61 3.55		2.21 2.18		53 57	
20 J. A.	M	17		1.58		3/12/41	Class II	On digitalis	64	233			0		74.5		3.13		1.98		49	
21 V. C.	M	34		1.76		3/12/42	Class II	On digitalis	82	211			-12.1		60.0		3.52		2.00		43	
22 J. R.	M	66		1.72 1.76		2/ 5/42 20/10/42	Class II Class III	On digitalis On digitalis	75 78	258 250			+18.9 +12.6		94.7 110.6		2.72 2.26		1.58 1.28		36 29	

TABLE III

SUBJECT	SEX	AGE	BODY SURFACE	DATE	FUNCTIONAL CAPACITY AND TREATMENT	HEART RATE	OXYGEN CONSUMPTION	B. M. R.	A-V O ₂ DIFFERENCE	CARDIAC OUTPUT	CARDIAC INDEX	SYSTOLIC OUTPUT	SYSTOLIC OUTPUT PER SQ. M.
		YR.	M. ²			PER MIN.	C.C. PER MIN.			LITERS PER MIN.	1/M. ² PER MIN.	C.C.	C.C./M. ²
Mitral Stenosis and Insufficiency, Aortic Insufficiency													
23 D. R.	F	47	1.56	19/ 9/42	Class II (Sinus rhythm) Without treatment	73	207	+ 6.6	65.6	3.16	2.02	43	27.5
Mitral Stenosis and Insufficiency, Tricuspid Stenosis and Insufficiency													
24 de C.	F	46	1.66	29/ 8/42	Class II (Auricular fibrillation) On digitalis	82	239	+15.8	74.0	3.23	1.95	39	23.7
25 M. de C.	F	50	1.47	23/ 2/45	Class IV (Auricular fibrillation) Without treatment	98	223	+22.2	97.4	2.29	1.56	23	15.9
Mitral Stenosis and Insufficiency, Interauricular Septal Defect													
26 L. de E.	F	39	1.55	6/ 4/42	Class II (Auricular fibrillation) On digitalis	58	226	+14.9	60.5	3.74	2.41	64	41.3
27 A. de C.	F	44	1.52	8/ 4/42	Class II (Auricular fibrillation) On digitalis	58	229	+17.2	56.0	4.09	2.64	70	45.2
28 A. de U.	F	39	1.62	10/ 9/42	Class II (Sinus rhythm) Without treatment	60	195	+ 3.3	61.2	3.19	2.10	53	35.0
				6/10/42	Class III (Auricular fibrillation) On digitalis	69	223	+ 9.3	83.5	2.67	1.65	38	23.5
				7/10/42	Class III (Auricular fibrillation) On digitalis	70	225	+10.1	92.5	2.43	1.50	34	21.0

TABLE IV

SUBJECT	SEX	AGE	DATE	FUNCTIONAL CAPACITY AND TREATMENT	HEART RATE	OXYGEN CONSUMPTION	B. M. R.	A-V O ₂ DIFFERENCE	CARDIAC OUTPUT	CARDIAC INDEX	SYSTOLIC OUTPUT	SYSTOLIC OUTPUT PER SQ. M.
		YR.			PER MIN.	C.C. PER LITER	%	C.C. PER LITER	LITERS PER MIN.	1/M. ² PER MIN.	C.C.	C.C./M. ²

Aortic Insufficiency

29	M	17	26/11/42	Class I Without treatment	76	284	+ 5.6	53.3	5.33	2.94	70	38.8
R. S.	M	53	12/ 2/43	Class III On digitalis	70	306	+19.2	68.2	4.49	2.27	64	32.3
B. N.			13/ 2/43	Class III On digitalis	70	306	+19.2	68.0	4.50	2.27	64	32.3

Aortic Stenosis and Insufficiency

31	M	60	20/ 4/43	Class II Without treatment	76	224	+ 3.5	62.9	3.56	2.10	47	27.8
M. P.			21/ 4/43	Class II Without treatment	76	219	+ 1.3	63.1	3.47	2.05	46	27.2
			20/ 5/43	Class II On digitalis	72	189	-12.4	58.7	3.22	1.91	45	26.5
32	M	42	13/ 8/42	Class III Without treatment	69	245	+19.4	86.7	2.82	1.83	41	26.5
A. C.			20/ 8/42	Class III Without treatment	65	227	+10.6	87.0	2.61	1.69	40	26.1

TABLE V. HYPERTENSIVE AND CORONARY HEART DISEASE

SUBJECT	SEX	AGE	BODY SURFACE	DATE	FUNCTIONAL CAPACITY AND TREATMENT	HEART RATE	OXYGEN CONSUMPTION	B. M. R.	A-V O ₂ DIFFERENCE	CARDIAC OUTPUT	CARDIAC INDEX	SYSTOLIC OUTPUT	SYSTOLIC OUTPUT PER SQ. M.
		YR.	M. ²			PER MIN.	C.C. PER LITER	%	C.C. PER LITER	LITERS PER MIN.	1/M. ² PER MIN.	C.C.	C.C./M. ²
33 M. P.	M	56	1.86	17/11/41	Class I (Auricular fibrillation) Without treatment	72	257	+ 8.0	50.5	5.09	2.73	71	38.0
			1.88	10/12/41	Class I (Auricular fibrillation) Without treatment	75	238	- 2.4	48.4	4.92	2.62	66	34.9
34 C. D.	M	70	1.95	2/10/42	Class II (Auricular flutter) Without treatment	54	240	- 1.1	56.6	4.24	2.17	78	40.0
				3/10/42	Class II (Auricular flutter) Without treatment	52	232	- 4.1	63.3	3.66	1.88	70	35.9
35 V. P.	M	59	1.85	22/ 5/43	Class II (Sinus rhythm) Without treatment	64	224	- 6.7	62.5	3.59	1.94	56	30.3
36 F. F.	M	59	1.77	13/ 9/44	Class II (Sinus rhythm) Without treatment	74	258	+12.5	64.6	3.99	2.25	54	30.5
				17/ 9/44	Class II (Sinus rhythm) Without treatment	70	264	+15.2	59.7	4.42	2.49	63	33.6
37 O. de R.	F	52	1.67	6/10/43	Class III (Auricular fibrillation) On digitalis	60	231	+14.3	85.6	2.70	1.62	45	26.9
38 D. P.	M	63	1.72	4/10/44	Class III (Sinus rhythm) Without treatment	80	237	+ 9.3	68.4	3.46	2.01	43	25.2
39 J. de C.	F	63	1.48	9/ 2/43	Class III (Auricular fibrillation) Without treatment	58	160	- 7.9	67.9	2.35	1.59	41	27.7
				10/ 2/43	Class III (Auricular fibrillation) Without treatment	56	167	- 4.1	71.8	2.32	1.57	41	27.7
40 M. de S.	F	68	1.48	5/12/42	Class III (Sinus rhythm) Without treatment	95	222	+27.9	77.8	2.85	1.93	30	20.3
41 C. A.	M	54	1.88	18/11/44	Class IV (Sinus rhythm) Without treatment	85	280	+14.9	92.0	3.04	1.62	36	19.1
			1.87	5/12/44	Class III (Sinus rhythm) On digitalis	67	242	0	64.9	3.73	1.99	56	29.9
42 I. de O.	F	51	1.59	29/ 4/43	Class IV (Auricular fibrillation) On digitalis	58	202	+ 3.7	93.9	2.15	1.35	37	23.3
				4/ 5/43	Class IV (Auricular fibrillation) On digitalis	80	224	+16.3	77.9	2.87	1.81	36	22.6

TABLE VI. AVERAGE RESULTS OBTAINED GROUPING THE CASES ACCORDING TO THEIR FUNCTIONAL CAPACITY

FUNCTIONAL CAPACITY	HEART RATE				ARTERIOVENOUS OXYGEN DIFFERENCE		CARDIAC INDEX		SYSTOLIC OUTPUT PER SQUARE METER OF BODY SURFACE	
	MITRAL GROUP		AORTIC, HYPERTENSIVE, AND CORONARY GROUP							
	NUMBER OF CASES	AVERAGE	NUMBER OF CASES	AVERAGE	NUMBER OF CASES	AVERAGE AND STANDARD DEVIATION	NUMBER OF CASES	AVERAGE AND STANDARD DEVIATION	NUMBER OF CASES	AVERAGE AND STANDARD DEVIATION
		PER MIN.		PER MIN.		L./M. ²		C.C./M. ²		
Class I	3	63	2	74	5	62.2 ±14.61	5	2.35 ±0.44	6	35.3 ± 6.90
Class II	19	70	4	66	23	66.9 ± 8.88	23	2.03 ±0.24	23	29.8 ± 5.50
Class III	6	83	7	71	12	81.0 ±13.71	12	1.73 ±0.30	13	23.8 ± 4.67
Class IV	1	98	2	77	3	91.8	3	1.58	3	19.3
Normal controls				63	17	60.4 ± 7.36	17	2.27 ±0.24	17	35.4 ± 3.14

normal and of the four cardiac groups is represented by a horizontal line, shows that the individual values are evenly distributed regardless of the diagnosis. In Table VI the results obtained by grouping the cases according to their functional capacity, disregarding their diagnosis, are presented.

DISCUSSION

The determination of cardiac output by a foreign gas method in patients with interauricular septal defect and mitral disease can be criticized, since in this condition the blood which passes from the left to the right auricle produces an abnormally rapid recirculation. We do not know whether or not in other similar cases this rapid recirculation can be an important source of error. In our patients it seems to have been of little importance since we could obtain similar values in two pairs of successive samples of the same rebreathing period.

Patient R. S. (uncomplicated aortic regurgitation, Class I, No. 29) showed a cardiac index well above the normal limit. Although the first possible explanation of this finding is a modification of the basal conditions, this could be ruled out because the patient was quiet and cooperative and the basal metabolic rate was normal. On the other hand, Starr and Gamble⁴⁸ stated that similar results have been obtained by Ewig and Hinsberg,¹⁸ Starr and collaborators,⁴⁷ Syllaba,⁶⁴ and Bock.⁶⁵ Even though the methods employed by some of these authors are open to objection, the fact that similar results were obtained by several investigators in patients without failure, where special technical difficulties are not expected, gives support to our findings.

Since the possibility exists that in aortic insufficiency the valvular defect might modify the cardiac index independently of the functional capacity, we eliminated patients with uncomplicated aortic insufficiency in calculating the average cardiac index of each functional group.

The difference between the cardiac index of normal subjects (2.27) and that of cardiac patients of Class I (2.35) is 0.08 ± 0.20 , which is not statistically significant. The difference between the average cardiac index of patients of Class I (2.35) and of patients of Class II (2.03) is 0.32 ± 0.20 , which likewise is not significant. Comparison of the normal persons (cardiac index, 2.27) with patients of Class II (cardiac index, 2.03) shows that the difference of the averages (0.24 ± 0.078) equals slightly more than three times its standard deviation, which is highly significant. Although the difference between patients in Class I and those in Class II is greater than that between normal persons and patients in Class II, it is not statistically significant in the former case because of the small number of patients in Class I (five patients). Comparison between the averages of individuals in Class II (cardiac index, 2.03) and those in Class III (cardiac index, 1.73) shows that the difference (0.30 ± 0.10) equals three times its standard deviation and is, therefore, statistically significant. Between persons in Class III (cardiac index, 1.73) and persons in Class IV (cardiac index, 1.58) the difference is 0.15. We did not determine a statistical difference with Class IV because of the small number of cases in the latter.

The results obtained in our series of hypertensive, coronary, and valvular diseases, excepting uncomplicated aortic regurgitation, led to the conclusion that the patients belonging to Class I (with no limitation of physical activity) maintain at rest a normal cardiac output. Patients of Class II (slight limitation of physical activity) on the whole have a diminished cardiac output even at rest, but their cardiac index is significantly greater than that of patients in Class III (marked limitation of physical activity). The small number of patients in Class IV (unable to carry on any physical activity without discomfort) prevented our drawing conclusions concerning this group, in spite of the low value of the average cardiac index, i. e., 1.58 liters per square meter per minute (the lowest value of any class). In patients with congestive heart failure, comparable to those included in Class IV, McGuire and his co-workers⁵⁸ found an average cardiac index of 1.52 ± 0.06 and Stewart and his associates⁶¹ found an index of 1.42. These results obtained with the acetylene method, taking three samples, give support to our findings and indicate that in patients in Class IV the cardiac output reaches its lowest level.

The normal values which we obtained in patients in Class I are in accord with the observations of McMichael⁵² made in the same type of patients and differ from the results of Stewart and his associates,⁶¹ who state that patients with organic heart disease without failure have a decreased cardiac index.

The above results show that most of the patients with heart failure have a diminished cardiac output and suggest that there is an inverse correlation between the degree of cardiac failure and the cardiac output. However, in some subjects, in spite of their cardiac failure, the cardiac output was within normal values, but this occurred less frequently in the more advanced stages of the disease. The possibility exists that, in some cases, even though there is a diminution of the cardiac output, the values reached are within the lower normal limits, for instance, an index of 2.5 to 2.0, the latter still being a normal figure. It is also possible that an increase in the metabolic rate, such as is frequently seen in heart failure, or variations in the other mechanisms which control the cardiac output (venous pressure, pulmonary ventilation, and so forth) may explain the differences found in the patients included in each class. The general trend of the cardiac output towards lower values in heart failure and the importance of the extracardiac factors are at present accepted by all investigators of this subject (Altschule,⁶⁶ McGuire and collaborators,⁵⁷⁻⁵⁹ McMichael,⁵² Harrison,⁵⁵ Stewart and his associates,^{60, 61} and others).

Some observers, however, notably Harrison and his co-workers⁵⁴ and Harrison,⁵⁵ believe that there is no correlation between the cardiac output and the degree of heart failure, and attribute this lack of correlation to the influence of the various extracardiac factors. On the other hand, several investigators (Stewart and collaborators^{60, 61} and McGuire and collaborators^{58, 59}) admit that a correlation can be drawn between cardiac output and the functional capacity of the heart, the exceptions being explained on the basis of extracardiac factors. Our findings support these conclusions. It should be emphasized that the correlation noted by Stewart and collaborators⁶⁰ between the number or type of valvular lesions and the functional alterations was not seen in our study.

The arteriovenous oxygen difference of patients in Class I (62.2 c.c. per liter) is approximately the same as that of normal subjects (60.4 c.c. per liter). The average values of the arteriovenous oxygen difference of patients of Class I and Class II (66.9 c.c. per liter) do not differ significantly (4.7 ± 6.79). On the other hand, the difference between the average values for patients of Class II and that of the normal persons is 6.5 ± 2.57 , which means that the difference is very probably real. The arteriovenous oxygen difference of patients in Class III (81.0) compared with patients in Class II shows a difference of 14.1 ± 3.37 , which is statistically significant. Patients in Class IV have an arteriovenous oxygen difference of 91.8, i. e., 10.8 greater than that of patients in Class III. No statistical determinations were carried out in Group IV because of the small number of cases.

These figures show that cardiac patients without failure maintain a practically normal arteriovenous oxygen difference. Where various degrees of failure exist, the arteriovenous oxygen difference increases, suggesting a correlation with the degree of the failure. The arteriovenous oxygen difference is an important index of the circulatory function. However, the wide scattering of the different values within normal as well as within cardiac groups makes necessary a great deal of caution in judging individual results.

The heart rate of patients with mitral stenosis shows a different behavior when compared with the behavior of the rate of patients with other types of heart disease. In calculating the averages in the group of patients with a mitral lesion, we excluded Case C. T. (mitral insufficiency and stenosis, sinus rhythm, No. 1, Class I) because of the slightly elevated metabolic rate which, in the absence of heart failure, indicated the possibility of a mild degree of hyperthyroidism. We considered +15 per cent to be the upper normal metabolic rate. For similar reasons we used only the fourth and fifth determinations made in Patient R. C. (mitral stenosis and insufficiency, auricular fibrillation, No. 15, Class II), whose basal metabolic rate was normal.

The results obtained show that in the cases with failure there was a general trend toward an increased heart rate, although there were differences within the various diagnostic groups. Patients with mitral valve lesions with no failure (Class I) showed a normal heart rate; those with various degrees of failure (Classes II, III, and IV) presented an increased cardiac rate which was proportional to the degree of the failure. On the other hand, in the other types of heart disease we could not observe any relation between functional capacity and heart rate.

The systolic output per square meter of body surface, up to now used almost exclusively by Scandinavian investigators, proved to be a useful index of circulatory modifications in heart failure. As the results did not show important differences in the various types of heart disease, it seemed reasonable to consider together all the cases of valvular, hypertensive, and coronary heart disease. The patients belonging to Class I had an average stroke volume per square meter of 35.3 c.c., nearly equal to that of normal subjects (35.4). Patients in Class II had a lower average (29.8), but the difference between patients in Class II and

those in Class I (5.5 ± 3.04) was not statistically significant. This may have been due to the small number of cases in Class I. The difference in stroke volume in normal persons and in patients in Class II was 5.6 ± 1.44 (statistically significant); the same holds for the difference between patients in Classes II and III (6.0 ± 1.73). Subjects in Class IV showed the lowest index (19.3), with a difference with respect to patients in Class III of 4.5. The figures suggest that an inverse correlation does exist between systolic output and the degree of heart failure.

SUMMARY AND CONCLUSIONS

The cardiac output under basal conditions was studied in forty-two patients with different types of valvular, hypertensive, or coronary heart disease, and in seventeen normal subjects. Grollman's acetylene method with four samples was used. The cardiac patients were grouped in four classes according to their functional capacity, following the criteria and nomenclature of the New York Heart Association. The following results, expressed as an average for each group, were obtained:

1. The cardiac index was 2.27 liters per square meter per minute ± 0.06 in the normal control group, 2.35 ± 0.19 in patients in Class I, 2.03 ± 0.05 in patients in Class II, 1.73 ± 0.087 in patients in Class III, and 1.58 in those in Class IV.

The differences found were statistically significant between the normal group and those in Class II, and between persons in Classes II and III, suggesting an inverse correlation between the degree of cardiac failure and the cardiac output.

2. The arteriovenous oxygen difference was 60.4 c.c. per liter of blood ± 1.78 in the normal group, 62.2 ± 6.53 in patients in Class I, 66.9 ± 1.85 in those in Class II, 81.0 ± 3.96 in persons in Class III, and 91.8 in patients in Class IV.

The difference between normal subjects and subjects in Class II was probably real, and the difference was statistically significant between subjects in Class II and subjects in Class III. This suggested a direct correlation between the degree of cardiac failure and the increase in arteriovenous oxygen difference.

3. The behavior of the heart rate was different in patients with mitral valve disease and in those with aortic, hypertensive, and coronary artery disease. The heart rate in the normal group averaged 63 per minute.

In the mitral patients the heart rate was 63 per minute in those in Class I, 70 in those in Class II, 83 in those in Class III, and 98 in Class IV. The heart rate in patients with other types of disease was 74 in those in Class I, 66 in those in Class II, 71 in those in Class III, and in 77 in patients in Class IV.

Although statistical determinations of these data were not carried out, the corresponding results in each group seemed to indicate that, in the mitral patients without failure (Class I), the heart rate was within the normal range, increasing in the presence of failure and according to the severity of the latter. In the aortic, hypertensive, or coronary groups, the behavior of the cardiac rate was rather irregular.

4. The systolic output per square meter of body surface was $35.4 \text{ c.c.} \pm 0.76$ in the normal group, 35.3 ± 2.81 in patients in Class I, 29.8 ± 1.14 in those in Class II, 23.8 ± 1.29 in those in Class III, and 19.3 in patients in Class IV.

The differences were statistically significant between the normal group and those in Class II and between patients in Classes II and III, suggesting that an inverse correlation exists between heart failure and systolic output.

We wish to express our gratitude to Dr. C. S. Burwell and his co-workers for teaching the technical details of the four-sample acetylene method to one of us (A. C. T.).

REFERENCES

1. Von Plesch, J.: Hämodynamische Studien, *Ztschr. f. exper. Path. u. Therap.*, Berl. 6: 380, 1909.
2. Lundsgaard, C.: Untersuchungen über das Minutenvolumen des Herzens bei Menschen. II. Patienten mit Herzklappenfehlern, *Deutsches Arch. f. klin. Med.*, Leipz. 118: 513, 1916.
3. Eppinger, H., von Papp, L., and Schwarz, H.: Ueber das Asthma Cardiale, Versuch zu Einer Peripheren Kreislaufpathologie, Berlin, 1924, Julius Springer.
4. Eppinger, H., Kisch, F., and Schwarz, H.: Das Versagen des Kreislaufes. Dynamische und energetische Ursachen, Berlin, 1927, Julius Springer.
5. Mobitz, W.: Die Ermittlung des Herzschlagvolumens des Menschen durch Einatmung von Äthyljodiddampf; IV. klinisch kompensierte Veränderungen des Herzens und der Gefäße und beginnende Kreislaufdekompensation ohne Lungenveränderungen, *Deutsches Arch. f. klin. Med.* 157: 359, 1927.
6. Mobitz, W.: Ergebnisse von 200 Herzschlagvolumbestimmungen beim Menschen, *Verhandl. d. deutsch. Gesellsch. f. inn. Med.* 38: 314, 1926.
7. Bansi, H. W., and Groscurth, G.: Die Kreislaufleistung während und nach der Arbeit beim gesunden und kranken Menschen, *Ztschr. f. Kreislaufforsch.* 22: 657, 1930.
8. Bansi, H. W., and Groscurth, G.: Die Bestimmung des zirkulatorischen Minutenvolumens mittels Acetylen (nach Grollman) in der Ruhe und bei Arbeitsversuchen, *Ztschr. f. d. ges. exper. Med.* 77: 631, 1931.
9. Bansi, H. W., and Groscurth, G.: Kreislauffunktionsprüfung bei Herzkranken, *Deutsche med. Wchnschr.* 57: 1276, 1931.
10. Means, J. H., and Newburgh, L. H.: Studies of the Blood Flow by the Method of Krogh and Lindhardt, *Tr. Ass. Am. Physicians* 30: 51, 1915.
11. Meakins, J. C., Dautrebande, L., and Fetter, W. J.: Influence of Circulatory Disturbances on Gaseous Exchange of Blood; the Blood Gases and Circulation Rate in Cases of Mitral Stenosis, *Heart* 10: 153, 1923.
12. Meakins, J. C., and Davies, H. W.: *Respiratory Function in Disease*, London, 1925, Oliver and Boyd, Ltd.
13. Dautrebande, L.: Physiopathologie du ralentissement circulatoire; ses rapports avec le débit cardiaque, *Arch. d. mal. du coeur* 21: 296, 1928.
14. Berconsky, I.: El volumen circulatorio por minuto en el estado normal y patológico, Buenos Aires, 1930, Emilio Spinelli.
15. Weiss, S., and Ellis, L. B.: Circulatory Measurements in Patients With Rheumatic Heart Disease Before and After the Administration of Digitalis, *J. Clin. Investigation* 8: 435, 1930.
16. Smith, W. C., Walker, G. L., and Alt, H. L.: The Cardiac Output in Heart Disease. I. Complete Heart Block, Auricular Fibrillation Before and After Restoration to Normal Rhythm, Subacute Rheumatic Fever and Chronic Rheumatic Valvular Disease, *Arch. Int. Med.* 45: 706, 1930.
17. Alt, H. L., Walker, G. L., and Smith, W. C.: The Cardiac Output in Heart Disease. II. Effect of Exercise on the Circulation in Patients With Chronic Rheumatic Valvular Disease, Subacute Rheumatic Fever and Complete Heart Block, *Arch. Int. Med.* 45: 958, 1930.
18. Ewig, W., and Hinsberg, K.: Kreislaufstudien, *Ztschr. f. klin. Med.* 115: 693, 1931.
19. Cossio, P., and Berconsky, I.: Insuffisance cardiaque inapparente, *Rev. sud-am. de méd. et de chir.* 4: 853, 1933.

20. Cordier, V., Enselme, J., and Nury, D.: Etude des échanges respiratoires et du débit cardiaque, *Lyon méd.* 158: 466, 1936.
21. Benedetti, P.: La portata circolatoria e la gittata sistolica in rapporto alla grandezza tridimensionale del cuore nei cardiopazienti, *Arch. di pat. e clin. med.* 17: 150, 1937.
22. Henderson, Y., and Haggard, H. W.: The Circulation and its Measurement, *Am. J. Physiol.* 73: 193, 1925.
23. Kininmonth, J. G.: The Circulation Rate in Some Pathological States, With Observations on the Effect of Digitalis, *Quart. J. Med.* 21: 277, 1928.
24. Lauter, S., and Baumann, H.: Zur Theorie der Herzinsuffizienz und der Digitaliswirkung, *Klin. Wchnschr.* 8: 263 1929.
25. Ringer, M., and Altschule, M. D.: Studies on the Circulation. II. Cardiac Output in Diseases of the Heart and Under the Influence of Digitalis Therapy, *AM. HEART J.* 5: 305, 1930.
26. Kroetz, C.: Messung des Kreislaufminutenvolumens mit Acetylen als Fremdgas. Ihre bisherigen Ergebnisse bei arteriellem Hochdruck und bei Dekompensation des Kreislaufs, *Klin. Wchnschr.* 9: 966, 1930.
27. Grassmann, W., and Herzog, F.: Die Wirkung von Digitalis (Strophanthin) auf das Minuten- und Schlagvolumen des Herzkranken, *Arch. f. exper. Path. u. Pharmacol.* 163: 97, 1931.
28. Stewart, H. J.: Effect of Giving Digitalis on the Volume Output of the Heart and its Size in Heart Failure, *Proc. Soc. Exper. Biol. & Med.* 29: 209, 1931.
29. Stewart, H. J., and Cohn, A. E.: Studies on the Effect of the Action of Digitalis on the Output of Blood From the Heart. III. Part 1. The Effect on the Output in Normal Human Hearts. Part 2. The Effect on the Output of Hearts in Heart Failure With Congestion in Human Beings, *J. Clin. Investigation* 11: 917, 1932.
30. Nylin, G.: Clinical Tests of the Function of the Heart, *Acta med. Scandinav., supp.* 52: 1, 1933.
31. Lyholm, E., Nylin, G., and Quarna, K.: The Relation Between the Heart Volume and Stroke Volume Under Physiological and Pathological Conditions, *Acta radiol.* 15: 237, 1934.
32. Oettinger, I., and Masel, I.: Schlag- und Minutenvolumen bei Mitralfehlern, *Deutsches Arch. f. klin. Med.* 177: 661, 1935.
33. Goldbloom, A. A.: Clinical Studies in Circulatory Adjustments. III. Clinical Evaluation of Cardiac Output Studies, *Internat. Clin.* 3: 206, 1936.
34. Goldbloom, A. A., and Lieberman, A.: Clinical Studies in Circulatory Adjustments. V. Clinical Evaluation of Cardiodynamic Studies, *Am. J. M. Sc.* 197: 182, 1939.
35. Nielsen, H. E.: Clinical Investigations Into the Cardiac Output of Patients With Compensated Heart Disease During Rest and During Muscular Work. *Acta med. Scandinav.* 91: 223, 1937.
36. Lequime, J.: Le débit cardiaque, études expérimentales et cliniques, *Acta med. Scandinav., supp.* 107: 1, 1940.
37. Espersen, T.: Studies on the Cardiac Output and Related Circulatory Functions, Especially in Patients With Congestive Heart Failure, *Acta med. Scandinav.* 108: 153, 1941.
38. Hamilton, W. F., Moore, J. W., Kinsman, J. M., and Spurling, R. G.: Studies on the Circulation; Further Analysis of the Injection Method, and of Changes in Hemodynamics Under Physiological and Pathological Conditions, *Am. J. Physiol.* 99: 534, 1932.
39. Kinsman, J. M., Moore, J. W., and Hamilton, W. F.: Studies on the Circulation: Analysis of Some Problems of the Circulation in Man in the Normal and in the Pathological States by the Use of the Injection Method, *Kentucky M. J.* 31: 285, 1933.
40. Kinsman, J. M., and Moore, J. W.: The Hemodynamics of the Circulation in Hypertension, *Ann. Int. Med.* 9: 649, 1935.
41. Starr, I.: Clinical Studies With the Ballistocardiograph; in Congestive Failure, on Digitalis Action, on Changes in Ballistic Form, and in Certain Acute Experiments, *Am. J. M. Sc.* 202: 469, 1941.
42. Starr, I., and Schroeder, H. A.: Ballistocardiogram. II. Normal Standards, Abnormalities Commonly Found in Diseases of the Heart and Circulation, and Their Significance, *J. Clin. Investigation* 19: 437, 1940.
43. Seymour, W. B., Pritchard, W. H., Longley, L. P., and Hayman, J. M., Jr.: Cardiac Output, Blood and Interstitial Fluid Volumes, Total Circulating Serum Protein, and Kidney Function During Cardiac Failure and After Improvement, *J. Clin. Investigation* 21: 229, 1942.
44. Lauter, S.: Kreislaufprobleme, *München. med. Wchnschr.* 77: 526, 1930.
45. Padilla, T., Cossio, P., and Berconsky, I.: Sondeo del corazón. III. Determinación del volumen minute circulatorio, *Semana méd.* 2: 445, 1932.

46. Starr, I., Jr., Collins, L. H., Jr., and Wood, F. C.: Studies of the Basal Work and Output of the Heart in Clinical Conditions, *J. Clin. Investigation* 12: 13, 1933.
47. Starr, I., Jr., Donal, J. S., Margolies, A., Shaw, R., Collins, L. H., Jr., and Gamble, C. J.: Studies of the Heart and Circulation in Disease; Estimations of Basal Cardiac Output, Metabolism, Heart Size and Blood Pressure in 235 Subjects, *J. Clin. Investigation* 13: 561, 1934.
48. Starr, I., Jr., and Gamble, C. J.: Cardiac Output in Common Clinical Conditions; and the Diagnosis of Myocardial Insufficiency by Cardiac Output Methods, *Ann. Int. Med.* 9: 569, 1935.
49. Starr, I., Jr., and Gamble, C. J., An Improved Method for the Determination of Cardiac Output in Man by Means of Ethyl Iodide, *Am. J. Physiol.* 87: 450, 1928.
50. Atschule, M. D., and Blumgart, H. L.: The Circulatory Dynamics in Tricuspid Stenosis; Their Significance in Pathogenesis of Edema and Orthopnea, *AM. HEART J.* 13: 589, 1937.
51. Grollman, A., Friedman, B., Clark, G., and Harrison, T. R.: Studies in Congestive Heart Failure. XXIV. A Critical Study of Methods for Determining the Cardiac Output in Patients With Cardiac Disease, *J. Clin. Investigation* 12: 751, 1933.
52. McMichael, J.: Output of Heart in Congestive Failure, *Quart. J. Med.* 7: 331, 1938.
53. Taquini, A. C., Suárez, J. R. E., and Fasciolo, J. C.: Capacidad funcional en la estenosis mitral, *Rev. Argent. de cardiol.* 9: 279, 1943.
54. Harrison, T. R., Friedman, B., Clark, G., and Resnik, H.: The Cardiac Output in Relation to Cardiac Failure, *Arch. Int. Med.* 51: 239, 1934.
55. Harrison, T. R.: Failure of the Circulation, Baltimore, 1939, Williams and Wilkins Company.
56. McGuire, J., Hauenstein, V., and Shore, R.: Cardiac Output in Heart Disease Determined by the Direct Fick Method, Including Comparative Determinations by the Acetylene Method, *Arch. Int. Med.* 60: 1034, 1937.
57. McGuire, J., Shore, R., Hauenstein, V., and Goldman, F.: Influence of Exercise on Cardiac Output in Congestive Heart Failure, *Arch. Int. Med.* 63: 469, 1939.
58. McGuire, J., Shore, R., Hauenstein, V., and Goldman, F.: Relation of Cardiac Output to Congestive Heart Failure, *Arch. Int. Med.* 63: 290, 1939.
59. McGuire, J., Shore, R., Hauenstein, V., and Goldman, F.: The Cardiac Output in Compensation and Decompensation in the Same Individual, *AM. HEART J.* 16: 449, 1938.
60. Stewart, H. J., Deitrick, J. E., Watson, R. R., Wheeler, C. H., and Crane, N. F.: The Effect of Valvular Heart Disease on the Dynamics of the Circulation. Observation Before, During and After the Occurrence of Heart Failure, *AM. HEART J.* 16: 477, 1938.
61. Stewart, H. J., Crane, N. F., Watson, R. F., Wheeler, C. H., and Deitrick, J. E.: The Cardiac Output in Congestive Heart Failure and in Organic Heart Disease, *Ann. Int. Med.* 13: 2323, 1940.
62. Grollman, A.: The Determination of the Cardiac Output of Man by the Use of Acetylene, *Am. J. Physiol.* 88: 432, 1929.
63. New York Heart Association, Criteria Committee: Nomenclature and Criteria for Diagnosis of Diseases of the Heart, N. Y. Tuberc. & Health Assoc., 1939.
64. Syllaba, J.: *Bull. int. Acad. Sci. Boheme. Prague*, 1934. Quoted by Starr, I., Jr., and Gamble, C. J.: *Ann. Int. Med.* 9: 569, 1935.
65. Bock, H. E.: Das Minutenvolumen des Herzens im Liegen und Stehen, *Ztschr. f. d. ges. exper. Med.* 92: 782, 1934.
66. Altschule, M. D.: The Pathological Physiology of Chronic Cardiac Decompensation, *Medicine* 17: 75, 1938.

RENIN IN ESSENTIAL HYPERTENSION

ALBERTO C. TAQUINI, M.D., AND JUAN CARLOS FASCILOLO, M.D.
BUENOS AIRES, ARGENTINA

THERE has been much discussion recently on the part which the kidney plays in the production of human hypertension. Recent work seems to indicate that renin is the pressor substance involved in the mechanism of renal hypertension. Renin has been found in the arterial and renal venous blood of dogs having hypertension of recent onset with severe reduction of the renal blood flow but not in the renal or arterial blood of chronically hypertensive dogs.¹ Using the method of Leloir and his co-workers² we were able, in 1943,³ to detect renin in two patients who had severe acute glomerulonephritis. These findings agree with those of Dexter and Haynes⁴ who, with a similar method, detected renin in one patient with eclampsia, two with severe pre-eclampsia, and one with fulminating glomerulonephritis, but not in patients with other types of hypertension.

It seemed appropriate to repeat these investigations, using for the detection of renin the indirect method of Muñoz and his associates.⁵ This method is capable of detecting about 0.1 unit of human renin in 10 c.c. of plasma. Its sensitivity is about five to ten times greater than the direct method of Leloir and his co-workers.²

MATERIAL AND METHODS

This investigation was carried out on twenty-three hypertensive patients. In all of them the diagnosis was essential hypertension. The existence of medical or surgical renal disease or of other known causes of hypertension were excluded as far as possible. The patients were observed over long periods of time, and several determinations of the blood pressure were made. The figure that appears in the table represents the average. All of the patients belonged to Groups II, III, and IV of the Keith, Wagener, and Barker classification.⁶ Seven patients were in Group II, eight were in Group III, and eight were in Group IV. Five patients in the last group were in an advanced stage of malignant hypertension and died soon after the estimation of renin was made.

Blood was taken in most cases by venous puncture and in some by arterial puncture. Sodium citrate or heparin was used to prevent coagulation. The blood was immediately centrifuged. The plasma was transferred to a tube and the determinations were carried out within a few hours. Sometimes the estimations were deferred for a day or two; the plasma was kept in the icebox in the meantime.

Center of Cardiologic Research, Virginio F. Grego Foundation. Faculty of Medicine, University of Buenos Aires, Buenos Aires, Argentina.
Received for publication Dec. 22, 1945.

For the detection of renin, the method of Muñoz and collaborators⁵ was used. The amount of renin is estimated by measuring the amount of hypertensinogen which it destroys during a four-hour incubation period. A measured amount of bovine hypertensinogen (about 1 unit) is incubated with 10 c.c. of the human plasma in which the determination is to be carried out; red cell hypertensinase and 0.6 c.c. of a 1 per cent solution of merthiolate (Lilly) as a preservative are added. A control tube is prepared in which human plasma and bovine hypertensinogen are incubated separately (Fig. 1).

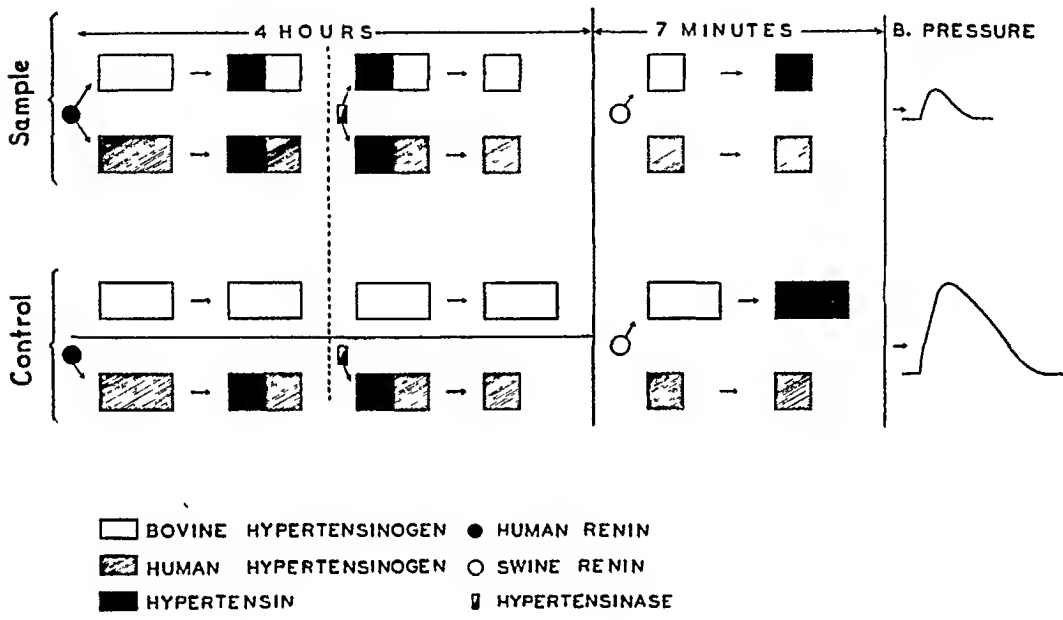


Fig. 1.—Diagram showing the reactions involved in the assay of human renin. The tube in which the determination is to be carried out is incubated four hours at 37°C. During this period, human renin, if present, transforms part of the hypertensinogen (bovine and human) into hypertensin, which will be destroyed by the hypertensinase present. These reactions have been represented in two steps, separated by the dotted line. Actually, they occur simultaneously. After the four-hour period, the bovine hypertensinogen left is estimated by incubating the plasma for seven minutes with swine renin which does not act upon human hypertensinogen. The hypertensin formed is estimated by its pressor effect when injected into an anesthetized dog intravenously. In the control tube, human plasma and bovine hypertensinogen are incubated separately. This is represented in the diagram by the horizontal line dividing the control.

During the four-hour incubation period, renin, if present, transforms part of the bovine and human hypertensinogen, and the hypertensin that is formed is destroyed by the hypertensinase. The bovine hypertensinogen remaining is then estimated; advantage is taken of the specificity of pig renin. An excess of pig renin transforms all of the bovine but none of the human hypertensinogen into hypertensin in seven minutes. Because of the short incubation time, the hypertensin formed is not destroyed by the hypertensinase. After precipitation with alcohol, the hypertensin content of each tube is estimated by the extent to which it raises blood pressure in the anesthetized dog. Fig. 1 presents a graphic description of the reactions involved.

By the use of the present method, amounts of renin as small as 0.1 unit* in 10 c.c. of plasma can be detected semiquantitatively. Three tubes were prepared. The first, hereafter referred to as the sample tube, contained the patient's plasma, bovine hypertensinogen, and hypertensinase, as described before. Tube 2 contained 10 c.c. of plasma, and Tube 3 contained the bovine hypertensinogen. The three tubes were incubated at 37°C. for a period of four to eleven hours, after which the contents of Tubes 2 and 3 were mixed to make the control tube. Three cubic centimeters of pig renin were added to the sample tube and to the control tube, and both were incubated for seven minutes. In other cases a fourth tube was added, containing human plasma (10 c.c.), bovine hypertensinogen, hypertensinase, and a measured amount of human renin (about 0.1 to 0.2 unit). We shall refer to this fourth tube as the standard tube. Determinations on the contents of this tube were carried out as in Tube 1.

After the short incubation period, the contents of the tubes were precipitated with 3 volumes of 95 per cent alcohol, the alcohol was distilled off *in vacuo*, and the aqueous residue was injected intravenously into an anesthetized dog. The blood pressure rises, in millimeters of mercury, were recorded on a smoked drum.

RESULTS

Table I summarizes the results. In every case the results are given according to the order in which the samples were injected into the dog. Since the sensitivity of the animal changes with time, as shown by the pressor response to a unit of hypertensin, it is important to know when the injection is made in order to compare the rise of pressure resulting from the injection of the solution in both the sample and control tubes.

The ratio $\frac{\text{mm. Hg rise of sample tube}}{\text{mm. Hg rise of control tube}} \times 100$ was calculated as follows: If the sample and the control tubes were tested, one immediately after the other, the rises in blood pressure were compared directly, even if the sensitivity of the dog changed, as indicated by a change in pressor response to 1 unit of hypertensin injected before and after the samples. If a standard tube containing renin was injected between the sample and the control tubes, the pressor response of both sample and control tubes was compared with the nearest hypertensin unit and the calculated ratio $\frac{\text{sample tube}}{\text{unit of hypertensin}}$ was compared as before. In the ratio $\frac{\text{standard with renin}}{\text{control tube}} \times 100$, the rises in blood pressure were directly compared.

For example, in Case A. de R., the rises in blood pressure in millimeters of mercury were as follows: unit of hypertensin = 30; sample tube = 15; standard with renin = 8; control = 16; hypertensin unit = 32. We first calculated the

*A unit of renin is the amount which, when incubated two hours with an excess of hypertensinogen, yields 0.5 unit of hypertensin.

TABLE I. RESULTS OF THE ASSAY OF HUMAN RENIN IN TWENTY-THREE PATIENTS WITH ESSENTIAL HYPERTENSION*

PATIENT	SEVERITY OF HYPER- TENSION (KEITH ET AL., 1939)	BLOOD PRESSURE OF PATIENT (SYSTOLIC AND DIASTOLIC)	BLOOD PRESSURE RISE PRODUCED BY								SAMPLE CONTROL × 100	STANDARD CONTROL × 100	TIME OF INCUBATION
			ONE UNIT OF HYPER- TENSIN	SAMPLE TUBE	STAND- ARD TUBE	ONE UNIT OF HYPER- TENSIN	CON- TROL TUBE	ONE UNIT OF HYPER- TENSIN	STAND- ARD TUBE	ONE UNIT OF HYPER- TENSIN			
	GROUP	MM. HG	MM. HG	MM. HG	MM. HG	MM. HG	MM. HG	MM. HG	MM. HG	MM. HG			HOURS
I. de G.	II	185/120	29	22		22	14				117		4
S. M.	II	200/120	22	25			18	20			139		4
R. N.	II	198/135	36	30			20				150		4
J. F.	II	190/126	56	50			47	40			106		4
J. L. de C.	II	220/130	40	30			25	30			112		4
A. de R.	II	220/140	30	15			16	32			100		4
M. C.	II	260/145	43	33			29			30	50		11
H. D. de F.	III	240/120	20	22			15				146		4
			30	23			23	30			100		4
J. M. de M.	III	260/150	45	36			35	48			103		4
M. C. de F.	III	245/140	56	33			23	34			114	100	4
A. F.	III	210/110	34	21		27§	30				70	47	4
L. A.	III	230/130	30	18		9	18	30			100	50	4
M. S.	III	240/120	30	30			27			50			11
M. G. de C.	III	250/100	50	30			26			34			11
A. L.	III	205/110	60	50			35				143	39	10
M. P. de C.	IV	235/140	33	17			17	33			100		4
J. T.	IV	280/160	40	15			14	40			107		4
M. de S.	IV	250/130	32	22		18	22				100	82	4
A. P.†	IV	245/135	60	40			32	70			125		10
C. M.†	IV	240/120	70	30			30				100		10
I. de M.†	IV	270/160	48	32			40	48			80		4
			48	40			30	40			111		4
F. E. G.†	IV	250/155	38	26		20§	24	38			108	67	4
			28	18		9†	20	32			103		4
D. M.†	IV	250/140	40	20			20			50	45		8

*The pressor responses are tabulated according to the order in which the samples were injected into the anesthetized dog.

†Malignant hypertension.

‡With 0.002 c.c. of a human renin solution containing 50 to 60 units per cubic centimeter.

§With 0.005 c.c. of a human renin solution containing 20 to 30 units per cubic centimeter.

||With 0.01 c.c. of a human renin solution containing 20 to 30 units per cubic centimeter.

ratio $\frac{\text{sample tube}}{\text{unit of hypertensin}} = \frac{15}{30} = 0.5$ and $\frac{\text{control tube}}{\text{unit of hypertensin}} = \frac{16}{32} = 0.5$, using the nearest value obtained for the unit of standard hypertensin. Then the ratio $\frac{\text{sample tube}}{\text{control tube}} \times 100 = \frac{0.5}{0.5} \times 100 = 100$ was calculated. For the ratio $\frac{\text{sample tube}}{\text{standard with renin}} \times 100 = \frac{8}{16} \times 100 = 50$, the rises were directly compared.

Table I shows that in 18 of the 26 cases, the ratio $\frac{\text{sample tube}}{\text{control tube}} \times 100$ ranged between 100 and 115, indicating that both tubes contained approximately the same quantities of hypertensinogen, which in turn indicates that renin was not present in the sample plasma. In two cases the diminution of the hyper-

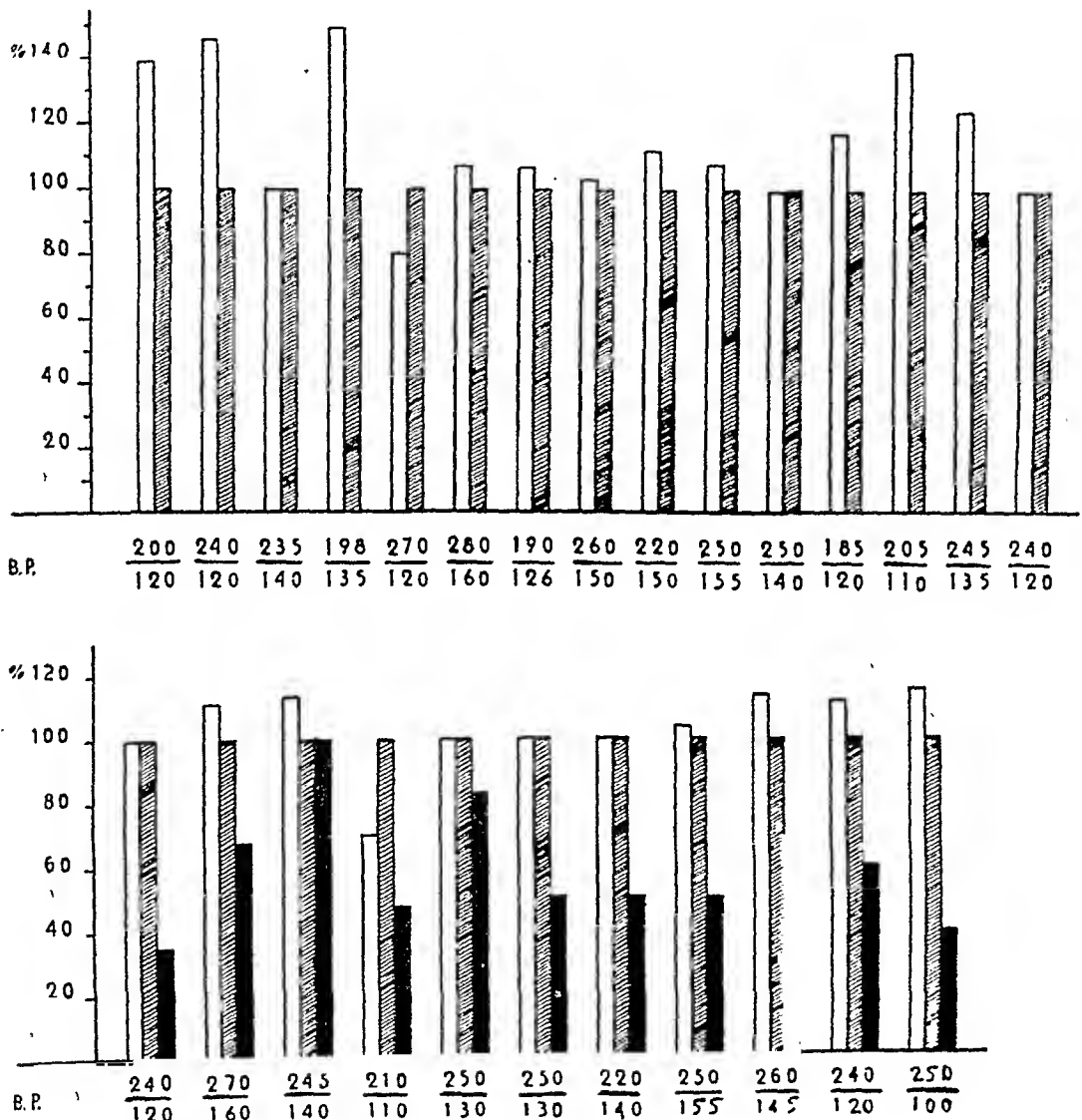


Fig. 2.—Ordinates represent the values of the $\frac{\text{sample}}{\text{control}} \times 100$ ratios. White columns are the ratios corresponding to the sample tubes; black columns represent the ratios of the tubes to which a small amount (0.1 to 0.2 unit) of human renin was added (standard tube). The shaded columns represent a ratio of 100. Values under 100 indicate the presence of renin. For interpretation of the data on the two patients in whom values were low, as indicated by short white columns, see text. The figures on the bottom of the columns are the values of the blood pressure of each patient.

tesinogen in the sample tube suggested the presence of renin. In one of them, however, a duplicate determination gave no indication of the presence of renin.

In six cases the ratio ranged between 117 and 150. This may have been due to changes in the sensitivity of the dog to hypertensin, especially in the extreme cases with a ratio of 146, 150, and 143. In these cases, no tests with the standard hypertensin unit were made after the injection of the control tube. On the whole, the results seem to indicate a small increase of pressor action in the sample tube. At present we are unable to explain these results.

All except one of the standard tubes with added human renin showed a ratio ranging from 82 to 35. This indicated that the minute amount of renin added (0.1 to 0.2 unit) was, with only one exception, easily detected.

DISCUSSION

Using the methods available, renin has not been detected in the plasma of patients in either the benign or the malignant phase of essential hypertension. These findings, however, do not disprove the renal origin of human hypertension. Actually, renin has been detected in the plasma of dogs after a short period of complete ischemia of the kidney,⁷ and in the renal and arterial blood in the acute phase of hypertension produced by partial but severe ischemia of the kidney.¹ On the other hand, renin has not been demonstrated in the renal or arterial blood of chronically hypertensive dogs.^{1, 8} In the human being, small amounts of renin were found in the renal vein after a short period of complete ischemia⁹ and in the acute hypertension of a few cases of eclampsia and fulminating glomerulonephritis⁴ but not in chronic hypertension. Since the results obtained in human hypertension agree with those obtained in experimental renal hypertension of the dog, we can conclude that the absence of renin cannot rule out the renal origin of essential hypertension.

The fact that it has not been possible to detect renin in the blood of chronically hypertensive dogs or of patients with essential hypertension neither supports nor negates the hypothesis that renin is the pressor substance involved. Whether renin is present in such minute amounts that it cannot be detected by the method used, or whether it does not exist at all in these patients, cannot be decided at present.

Since renin is found by existing methods in the acute phase of renal hypertensive disease and in complete ischemia of the kidney but not in the chronic stage of the disease, the possibility exists that renin may appear in the blood as an autolytic product of the kidney. It is also possible that renin may initiate the pressor mechanism which later proceeds without its presence.

CONCLUSIONS

Renin has not been detected in the arterial or venous plasma of twenty-three patients suffering from essential hypertension with and without impairment of renal function.

REFERENCES

1. Dell'Oro, R., and Braun-Menéndez, E.: Dosaje de renina en la sangre de perros hipertensos por isquemia renal, *Rev. Soc. argent. de biol.* 18: 65, 1942.
2. Leloir, L. F., Muñoz, J. M., Braun-Menéndez, E., and Fasciolo, J. C.: Dosaje de la renina, *Rev. Soc. argent. de biol.* 16: 635, 1940.
3. Braun-Menéndez, E., Fasciolo, J. C., Leloir, L. F., Muñoz, J. M., and Taquini, A. C.: Hipertensión Arterial Nefrógica, El Ateneo, Buenos Aires, 1943.
4. Dexter, L., and Haynes, F. W.: Relation of Renin to Human Hypertension With Particular Reference to Eclampsia, Preeclampsia and Acute Glomerulonephritis, *Proc. Soc. Exper. Biol. & Med.* 55: 288, 1944.
5. Muñoz, J. M., Taquini, A. C., Braun-Menéndez, E., Fasciolo, J. C., and Leloir, L. F.: Método para la medición de la renina humana, *Rev. Soc. argent. de biol.* 19: 321, 1943.
6. Keith, N. M., Wagener, H. P., and Barker, N. W.: Some Different Types of Essential Hypertension: Their Course and Prognosis, *Am. J. M. Sc.* 197: 332, 1939.
7. Taquini, A. C., and Braun-Menéndez, E.: Liberación de renina por el riñón totalmente isquemiado, *Rev. Soc. argent. de biol.* 17: 465, 1941.
8. Taquini, A. C., and Fasciolo, J. C.: Unpublished data.
9. Quinby, W. C., Dexter, L., Sandmeyer, J. A., and Haynes, F. W.: The Renal Humoral Pressor Mechanism in Man. II. The Effect of Transitory Complete Constriction of the Human Renal Artery on Blood Pressure and on the Concentration of Renin, Hypertensinogen, and Hypertensinase of Renal Arterial and Venous Blood, With Animal Observations, *J. Clin. Investigation* 24: 69, 1945.

PARASTERNAL LEADS IN TRICUSPID INSUFFICIENCY

GEORGE M. ELLIS, M.D., AND N. WORTH BROWN, M.D.
TOLEDO, OHIO

THE purpose of this communication is to illustrate the electrocardiograms of two cases presenting clinical signs of tricuspid insufficiency and right auricular enlargement. In these cases, striking and unusual auricular deflections of the diphasic (+ —) type are found in leads from the right side of the precordium. Their mode of production and possible significance have been a source of interest and speculation to us and will be discussed.

Unusual P waves in the precordial electrocardiogram have been the subject of only a few previous papers. Burton and Mehlman¹ published a report of a case of spontaneous pneumothorax of the right side of the chest in which a deeply inverted P wave (13 mm.) occurred in Lead CF₂. Upon partial release of the pneumothorax and during spontaneous resolution, this precordial P wave became diphasic and had a configuration similar to those described in the present report. Gertz,² also, reported a diphasic P wave in a lead taken at the C₂ position in a case in which a calcareous tuberculous lesion of the upper left lung caused traction on the heart. These cases differ, it will be noted, from the two we describe in that an extracardiac factor produced displacement of the heart toward the left and thus placed the right auricle beneath the area of the precordial electrode. Auricular deflections of this sort have apparently not been observed in the frequent clinical combination of cardiac decompensation with right pleural effusion and displacement of the heart toward the left.

Pardee³ has reported two cases of uncomplicated tricuspid stenosis with high, peaked P waves in the limb leads and discussed the findings of Winternitz who relates the size and shape of these waves to auricular hypertrophy. Pardee concludes that the height of the wave in limb leads is due to right auricular hypertrophy, and that the notching and increased duration is due to involvement of both auricles.

Szekely⁴ recently found no correlation between the size of the right auricle and the amplitude of the P waves as recorded in chest leads taken at the third intercostal space to the right of the sternum. He suggested as possible factors the anatomic position of the right auricle and its juxtaposition to the anterior chest wall.

A case of mitral stenosis and one of congenital heart disease, in which the electrocardiograms show an auricular complex in CF₁ similar to those in our cases, are illustrated by Sigler.⁵ The P waves were large and of the diphasic (+ —) type. Both of his cases showed right ventricular dilatation and hypertrophy.

From the Department of Medicine and the Heart Station of The Toledo Hospital, Toledo, Ohio.
Received for publication Dec. 24, 1945.

CASE REPORTS

CASE 1.—D. F., a white child, aged 12 years, was admitted to the pediatric floor of Toledo Hospital on Nov. 3, 1945. About three weeks previously, she had had an attack of "flu" from which she had made a satisfactory recovery. About four days prior to admission she rapidly became edematous, dyspneic, and cyanotic.

The past history was essentially negative with the exception of pneumonia in infancy. There had been no primary or secondary manifestations of rheumatic fever. She had been a perfectly normal child with no evidence of congenital heart disease.

Physical examination at the time of admission revealed a well-developed and well-nourished child, acutely and severely ill. The temperature was normal, the heart rate was 90, and the respirations were 22 per minute. Breathing was very difficult in the semiupright position and was accompanied by an expiratory grunt. The lips and nail beds were moderately cyanotic. The face appeared swollen, although the eyelids were not specifically edematous. The tonsils were hypertrophic, but the mucous membranes of the nose and throat were clear. The tongue was dry and furrowed. The neck was puffy and flaccid. No enlargement of the thyroid gland and no adenopathy were present. The jugular veins were not conspicuous. Examination of the lungs by percussion and auscultation revealed no changes, although the diaphragm was somewhat elevated on both sides.



Fig. 1.—Case 1. A-P and lateral roentgenograms.

Examination of the heart showed the rate to be rapid and the rhythm regular. The apical impulse was displaced upward and to the left. A presystolic gallop and a blowing systolic murmur, most marked at the apex, were noted. The sounds were very forceful. An abdominal fluid wave and shifting dullness gave evidence of ascites. There was edema of the right labium, sacrum, and lower extremities. The blood pressure was 110/65.

Other laboratory studies showed 3-plus albuminuria, many hyaline casts, a normal red count and hemoglobin, a leucocytosis of 32,000 with a differential of 52 segmented polys, 25 band forms, 20 mature lymphocytes, 2 monocytes, and 1 eosinophile. The nonprotein nitrogen was 57.3 mg. per cent, and a total protein determination was 5.8 Gm. per cent with 2.5 Gm. of albumin and 3.3 Gm. of globulin (albumin-globulin ratio: 0.76).

Paracentesis was performed, and 1,100 c.c. of cloudy, amber fluid with a specific gravity of 1.013 was withdrawn. This failed to relieve the dyspnea. Two days later her cardiac finding

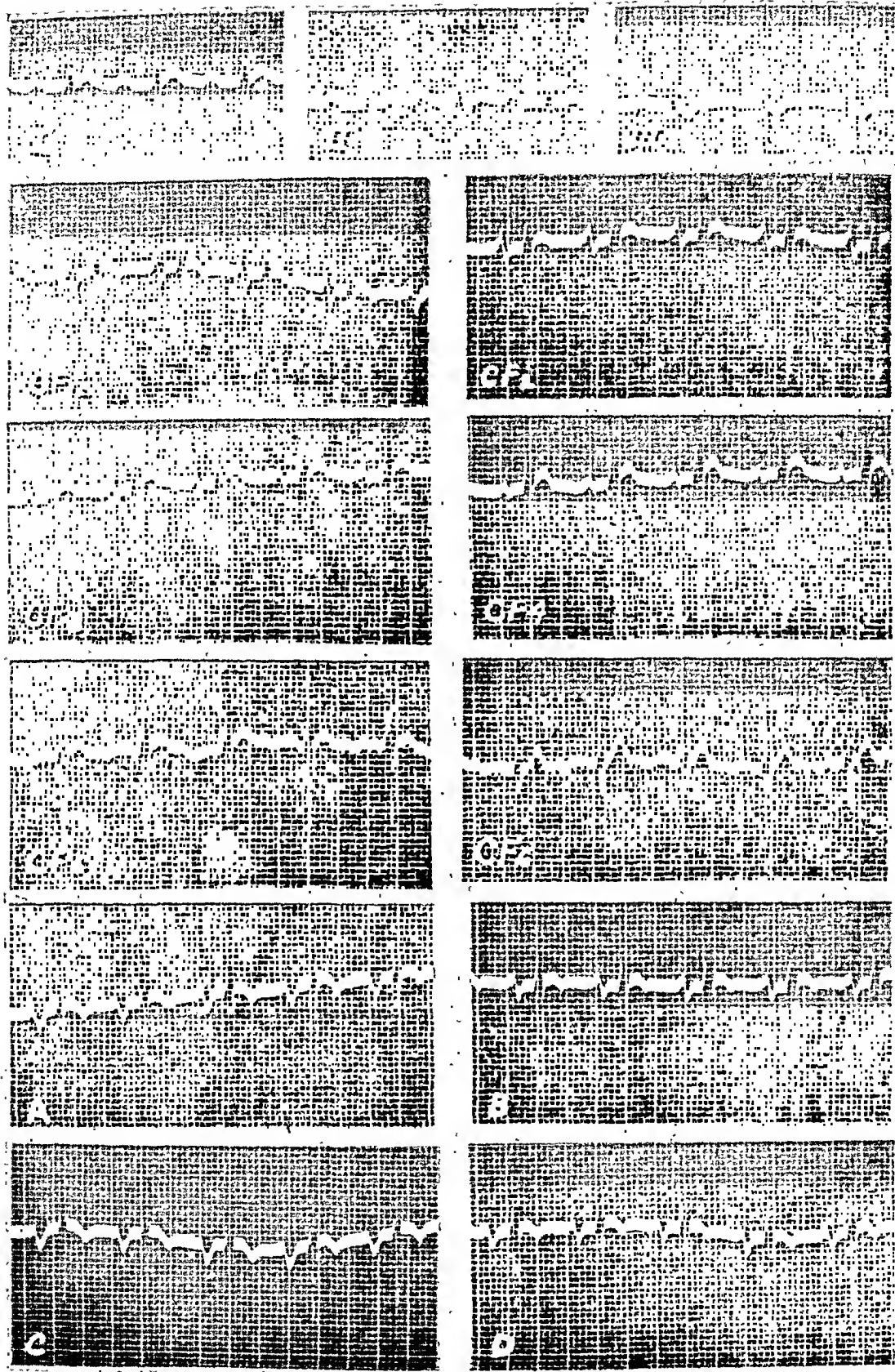


Fig. 2.—Case 1. Conventional leads, taken Nov. 11, 1945, show delayed auriculoventricular conduction time (0.24 second). Precordial leads were taken November 13. Note diphasic P waves in CF_1 and CF_2 . A, Third intercostal space to the right of the sternum. B, Third intercostal space to the left of the sternum. C, Second intercostal space to the right of the sternum. D, Second intercostal space to the left of the sternum. In these special precordial leads the left leg was used as the site of the indifferent electrode.

had become more definite, and fluoroscopic examination showed uniform pulsations of all borders of the heart. X-ray films of the chest (Fig. 1) were taken, and she was digitalized with marked improvement.

Subsequent laboratory determinations revealed no albuminuria, sedimentation rates of 8 and 15 mm., improvement in plasma proteins, normal urea nitrogen, and normal blood counts. A right pleural effusion developed but rapidly subsided, and this was not present when the electrocardiograms (Fig. 2) were taken.

On November 21, the following observations were recorded: By palpation the apical impulse is at the anterior axillary line. A short systolic thrill is felt in the left fourth intercostal space just within the mammary line. No thrills could be felt over the pulmonic valve area or in the neck over the carotids. There is a loud systolic murmur over the precordium. This murmur is loudest in the mitral area but is transmitted into the infra-axillary space, and posteriorly to the subscapular area. Systolic and diastolic murmurs are heard in the aortic area and down the left border of the sternum. Systolic and diastolic murmurs are heard in the tricuspid area also. The latter murmurs blended with the dominant murmurs, but because of the enlargement of the liver and its expansile systolic pulsation, were believed to be of tricuspid origin.

The diagnostic impressions were: (1) aortic regurgitation with possibly some stenosis, (2) mitral regurgitation with possibly some stenosis, and (3) tricuspid regurgitation. The lesions were evidently the result of a recent carditis involving chiefly the aortic and mitral valves complicated by a relative tricuspid insufficiency.

CASE 2.—S. W. J. was an 18-month-old boy. The history as related by the parents told of a normal delivery with no physical defects discovered by the attending physician. No respiratory disturbance nor cyanosis was noticed by the family. At the age of 9 months the child contracted a severe throat infection which necessitated three weeks' hospitalization. After discharge, he suffered a relapse with pulmonary complications. At this time his physician noticed a loud heart murmur which is said to have gradually increased in intensity during and after this illness. Six months ago another physician made the diagnosis of congenital heart disease, which was substantiated with frontal and lateral x-ray films.

On Nov. 11, 1945, the child was examined at the Toledo Clinic. At that time he appeared healthy and well nourished but somewhat backward in both physical and mental development. The chest was of normal shape and symmetrical. There was a large, diffuse impulse visible over the precordium, with the point of maximal intensity in the anterior axillary line. By percussion the right border was 3 to 4 cm. to the right of the sternal margin; the right costophrenic angle was not obliterated. There were no thrills over the precordium or carotids. The liver was of normal size, and the spleen could not be palpated. A long, loud, and rather harsh systolic murmur could be heard over the precordium and was well transmitted into the axilla and also heard posteriorly in the interscapular space. There was also a systolic and early, high-pitched, diastolic murmur of an entirely different tonal quality which was localized to a relatively small area over the lower sternum and the left fourth and fifth intercostal spaces. There was no presystolic element connected with any of these murmurs. During inspiration there was a reduplication of the second sound which was heard best in the second left intercostal space. The pulse rate at the time of the examination was 130 per minute. Arterial pulsation could easily be felt in the popliteal space. The hemoglobin was 96 per cent (Sahli), the red cell count was 5,310,000, and the leucocytes numbered 16,150. A single blood culture was negative. Frontal and lateral x-ray films showed a large globular heart (Fig. 3). The most conspicuous feature was the enlargement of the right auricle and right ventricle. The roentgenogram supported the clinical diagnosis of a congenital heart, the chief lesion being an interventricular septal defect. The electrocardiogram is illustrated in Fig. 3.

It seemed probable that the localized, high-pitched murmur was due to a relative tricuspid insufficiency. Although no enlargement of the liver could be demonstrated, x-ray films showed enlargement of both the right auricle and right ventricle so clearly that relative insufficiency of the tricuspid valve was considered a proper assumption.

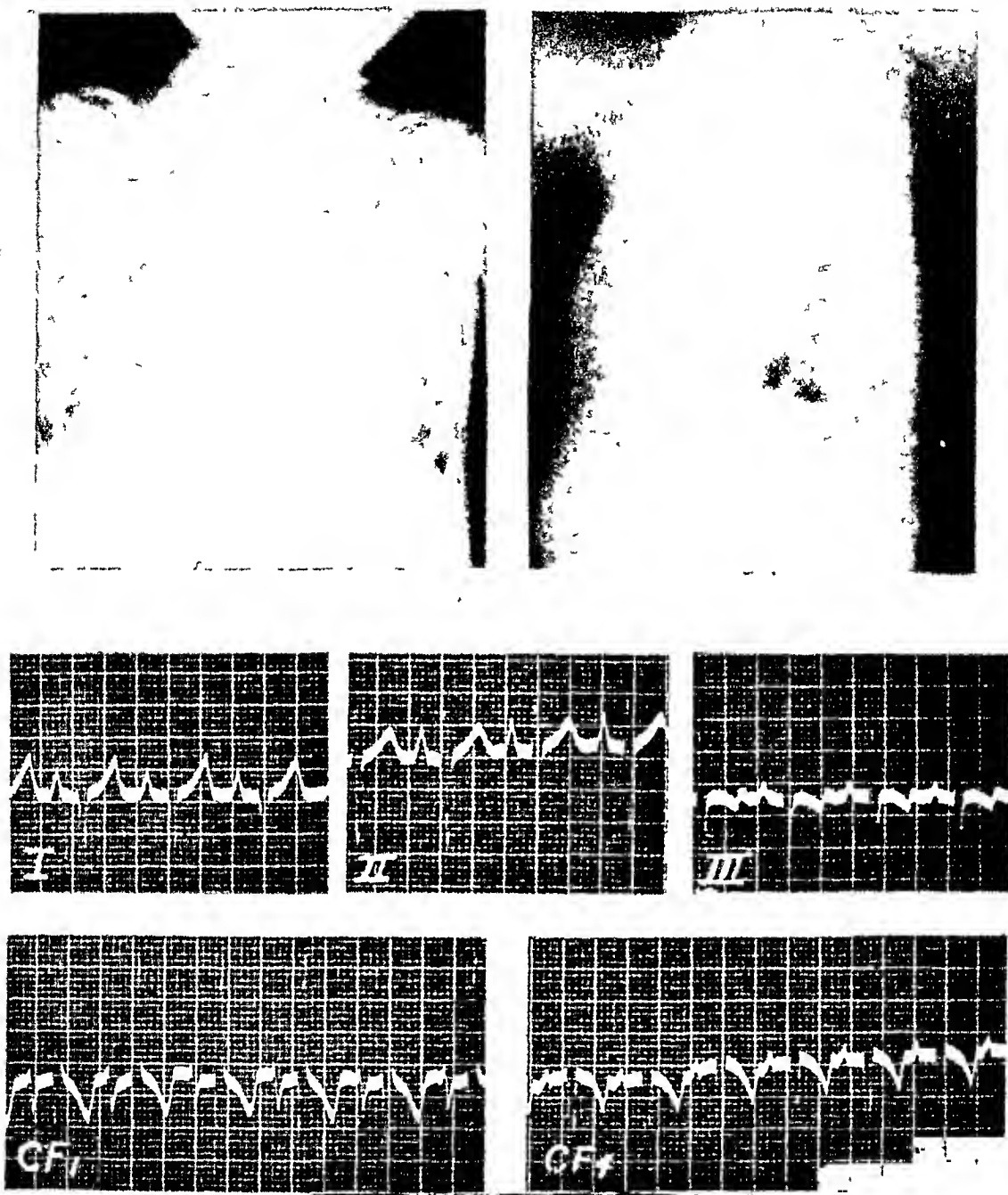


Fig 3—Case 2 A-P and lateral (52 inch) roentgenograms. Conventional leads, tall, peaked P waves in I and II, QRS complexes of large amplitude. Note diphasic P wave in CF_1 .

DISCUSSION

Attention is directed to the auricular deflections in Lead CF_1 of both cases. They consist of large, diphasic (+ —) waves with a sharp transition between the positive and negative components (Fig. 4).

These large, diphasic P waves are strikingly similar to auricular complexes seen in esophageal leads. They are also similar in contour to the P waves ob-

tained by Lewis⁶ and Wilson, Macleod, and Barker⁷ when an electrode was placed on the exposed auricle of a dog. As the peak of maximum positivity of the auricular complex represents the arrival of the excitation wave directly beneath the exploring electrode, we attempted in Case 1 to obtain varying proportions of positivity and negativity by taking parasternal leads from the third and second intercostal spaces; that is, from points nearer to the sinoauricular node. These are illustrated in Fig. 2.

From the character of the auricular complex in Case 2, it would seem that the electrode must have been so placed on the chest as to be in close proximity to the upper portion of the right auricle and not far from the sinoauricular node. This would account for the small initial positivity, the early downward stroke, and the prominent negative component.

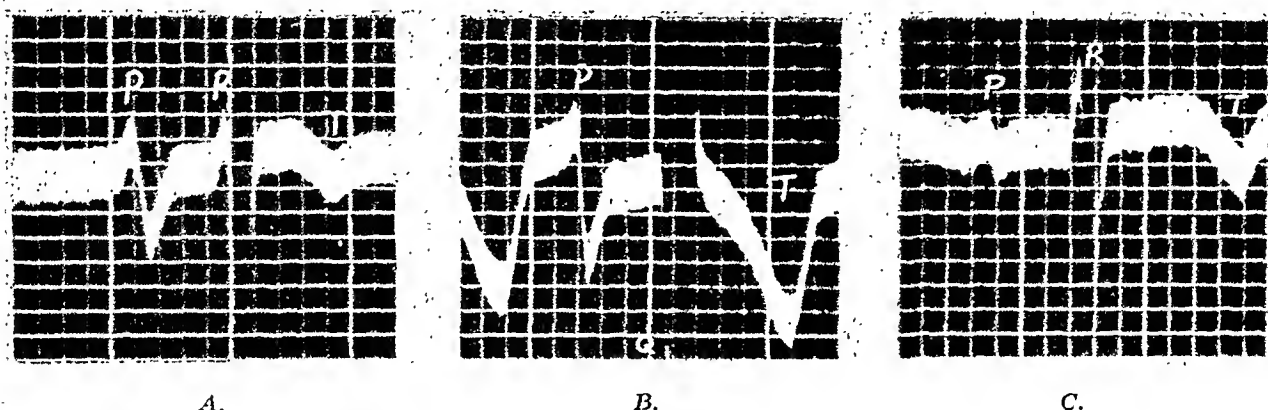


Fig. 4—Photographic enlargements illustrating the size and shape of the auricular complexes in Lead CF_1 . A, Case 1; B, Case 2; C, Lead CF_1 in normal 11-year-old child for comparison.

SUMMARY

Two cases are presented with clinical and x-ray findings of hypertrophy and dilatation of the right ventricle and right auricle, associated with tricuspid insufficiency. The electrocardiograms show large, diphasic P waves in Lead CF_1 such as are normally obtained from esophageal leads and experimentally in direct leads from exposed auricles. It is probable that the proximity of the enlarged right auricle to the anterior chest wall is largely responsible for an auricular wave of this type. Further observations may show that, in tricuspid insufficiency and right auricular enlargement, this characteristic auricular complex in parasternal leads is a significant diagnostic sign.

REFERENCES

1. Burton, S. D., and Mehlman, J. S.: An Unusual P Wave in Chest Lead CF_2 . Following Spontaneous Pneumothorax, *J. Lab. & Clin. Med.* 27: 465, 1942.
2. Gertz, G. F.: An Unusual P Wave in Lead IV, *AM. HEART J.* 15: 498, 1938.
3. Pardee, H. E. B.: Clinical Aspects of the Electrocardiogram, ed. 4, New York, 1941, Paul B. Hoeber, Inc., pp. 77-80.
4. Szekely, P.: Chest Leads for the Demonstration of Auricular Activity, *Brit. Heart J.* 6: 238, 1944.
5. Sigler, L. H.: The Electrocardiogram, New York, 1944, Grune and Stratton, Inc., p. 380.
6. Lewis, T.: Lectures on the Heart, New York, 1915, Paul B. Hoeber, Inc., pp. 8-16 and Fig. 9.
7. Wilson, F. N., Macleod, A. G., and Barker, P. S.: The Distribution of Currents of Action and Injury Displayed by Heart Muscle and Other Excitable Tissue, Ann Arbor, 1933, Univ. Mich. Press, pp. 8-12 and Fig. 3.

PERSISTENCE OF THE JUVENILE PATTERN IN THE PRECORDIAL
LEADS OF HEALTHY ADULT NEGROES, WITH REPORT OF
ELECTROCARDIOGRAPHIC SURVEY ON THREE HUNDRED
NEGRO AND TWO HUNDRED WHITE SUBJECTS

CAPTAIN DAVID LITTMANN, M.C.
ARMY OF THE UNITED STATES

THE genesis of the T wave in the normal electrocardiogram is still somewhat of a moot point. Irrespective, however, of whether the T wave is the result of organized electrical regression in the ventricles or of the geometric inequality of the complexes derived from the left and the right ventricles, most observers are in agreement that it is upright in electrocardiograms derived from the left side of the chest in adults.¹ The literature contains numerous excellent surveys on large groups of normal individuals which confirm this observation; a few of these will be reviewed briefly.

In 1936, Shipley and Halloran² examined the electrocardiograms of 200 normal men and women between the ages of 20 and 35 years and noted that T₄ was inverted in all instances.* Skulasen and Larsen³ made a similar study of patients between 30 and 50 years of age and found that the T waves from the chest leads were consistently upright. Wood, Wolferth, and Miller⁴ studied 299 college students and found three diphasic and one inverted T₄. The latter was in a young man with aortic insufficiency; all the other subjects were normal. In a similar manner, Graybiel and his co-workers⁵ made five-lead electrocardiograms (Leads I, II, III, IV F, and IV R) on 1,000 healthy aviators and noted two diphasic T waves in Lead CF₄ and none in Lead CR₄. There were no negative T waves.

When the use of chest leads became common, it was soon apparent that in children the T waves derived from the left side of the chest were very frequently opposite in direction to those obtained from similar positions in adults. The cause of this phenomenon has been studied extensively by various investigators. Since much of this work was done by the old technique in which the adult T₄ is normally inverted, it will be less confusing if we employ wherever possible, and at least during this phase of the discussion, the terms juvenile and adult rather than inverted and upright waves.

Rosenblum and Sampson⁶ studied 66 adults and 50 children and noted abnormal T waves in three of the adults. One was in a 16-year-old girl; the other two diverged only slightly from normal. Two of the 50 children demonstrated adult patterns and these were in subjects aged 14½ and 15 years. Dwan and

Received for publication Jan. 19, 1946.

*When this study was made, the technique used was such that an inverted T₄ was normal.

Shapiro⁷ studied several hundred children with normal and diseased hearts. They reported a high incidence of the juvenile form and, among other conclusions, stated that the findings in routine four-lead electrocardiograms appeared to be constant from day to day. Deeds and Barnes,⁸ who examined 50 normal men and a similar group of women, found one subject in whom the T wave in Lead CR₂ approached negativity, while in the other precordial positions the T wave was positive. They concluded that the juvenile form in subjects older than 15 years was to be considered abnormal. Master, Dack, and Jaffe⁹ noted juvenile electrocardiograms in 60 per cent of a group of children between the ages of 2 and 15 years. Only 5 per cent of juvenile patterns appeared in the group between 11 and 15 years of age. They suggested that the difference between the adult and juvenile forms was the result of earlier predominance of the right ventricle and of the normally greater relative anteroposterior diameter of the chest in children.

Robinow, Katz, and Bohning¹⁰ noted that juvenile patterns were more frequently found in children who had a thin chest wall and narrow thorax and less commonly in those with a more nearly adult type of chest. They made an exhaustive study of the problem and suggested reasons for the differences noted between adult and juvenile tracings. The known physical differences considered in their paper included the relative right ventricular predominance and axis rotation, the tendency for the heart to lie more horizontally, the greater proportion of the right ventricle lying in the area of left precordial dullness, and the more intimate contact of the heart with the chest wall. All of these are present in childhood. Since the configuration of the tracing is thought to be dependent, to a large extent, upon the conductivity of the tissues interposed between the heart and the chest wall, and since the chest electrode is placed in relation to the bony framework, it does not, therefore, bear the same relation to the heart in children as it does in adults.

The authors suggested that "The variations of T₄ in normal different children could be explained on the variable degrees of transition from the 'puerile' to 'adult' chest type." The same observers also studied electrocardiograms obtained from 20 normal children after a lapse of six to eight months and noted changes toward the adult form in seven instances and away from it in three.

Thus far, reasonable evidence has been obtained from the literature that in adults the T waves in leads derived from the left side of the precordium are normally upright, while in children they are frequently inverted. The theories advanced in explanation of this phenomenon are concerned largely with the differences between adult and juvenile hearts and chests, and the resultant change in relationship of the heart to the chest wall and exploring electrode. However, a number of instances of T₄ abnormality in adults with and without evidence of heart disease have also been noted.

Edeiken, Wolferth, and Wood¹¹ noted 26 instances of abnormal T₄ in adults in whom the other leads were normal. All of their patients, however, had some type of organic disease. They felt that an abnormal T₄ should not be disregarded and should be an indication for additional study for evidence of heart disease.

They concluded that they had not yet seen an abnormal T_4 in an adult in whom they were confident that "there was no significant heart disease."

Sodeman¹² reported an instance of a reversal of T_4 in a 26-year-old nurse without other evidence of disease. Shanno¹³ recorded his observations on electrocardiograms of 100 student nurses, aged 18 to 22 years. There were six instances of T-wave negativity in Lead CF_2 , one in Lead CF_3 and none in Lead CF_4 . No explanation was offered by either Shanno or Sodeman for these anomalies. Pardee,¹⁴ who observed occasional abnormalities in one chest lead, recommended the use of multiple leads and further observation in such cases.

Dupuy¹⁵ reported five cases of T-wave abnormalities in apparently normal soldiers. Several had T_4 changes, but these were invariably associated with abnormalities in T_1 and T_2 and occurred in individuals who had some type of cardiovascular complaint. Some of the tracings were grossly abnormal but were considered to be functional variants because they were reversible following rest and sedation. He suggested that these variants might be due to cardiac rotation or to anxiety associated with a rapid cardiac rate.

Thompson¹⁶ described interesting electrocardiographic changes which occurred during hyperventilation in susceptible individuals. Here, too, alterations were observed in the T waves of any or all leads in subjects with anxiety neuroses, precordial pain, tachycardia, and hyperventilation. This was considered to be the result of associated alkalosis. It is not improbable, however, that the anomalies recorded by both Dupuy¹⁵ and Thompson¹⁶ during anxiety, tachycardia, and hyperventilation were in some manner associated with coronary vasoconstriction in preclinical heart disease. Thompson considered this possibility.

In a similar manner Katz¹⁷ and McGuire¹⁸ have observed reversible T-wave changes in nervous individuals. Graybiel, Starr, and White¹⁹ have also noted S-T interval and T-wave changes resulting from the inhalation of tobacco smoke. The T-wave inversions following the ingestion of ice water are well known.

On the whole, however, the number of adults exhibiting T-wave inversion in the precordial leads in the absence of demonstrable heart disease is comparatively small.

In reviewing over 3,000 electrocardiograms made during a one-year period at an Army installation, a small number of T_4 inversions was noted. But, with three exceptions, these were all associated with organic disease of the heart and/or pericardium or occurred during the course of acute rheumatic fever. The three exceptions were extensively studied, but no evidence of heart disease was ever demonstrated. All three exceptions were in Negroes. This observation suggested a preponderance of the anomaly among Negroes, and since a review of the literature failed to reveal any large scale study of electrocardiograms of normal adult or juvenile Negroes, such a survey was undertaken.

MATERIAL AND METHODS

The instruments used in this study were Sanborn cardiettes which were frequently calibrated and compared. All tracings were made with the subject

TABLE I. PHYSICAL DESCRIPTION, HISTORY, AND LABORATORY FINDINGS IN SUBJECTS WHO DEMONSTRATED T₁ ABNORMALITY

AGE (YR.)	SEX	HEIGHT IN INCHES	WEIGHT IN POUNDS	USE OF DRUGS	HISTORY OF RECENT ILLNESS	HISTORY OF RHEU- MATIC FEVER	HISTORY OF SCARLET FEVER	KAHN REAC- TION	HEMO- GLOBIN	SEDIMEN- TATION RATE MM./HR.*	SICKLE CELLS	HEART SIZE DEVIATION BY X-RAY†	BLOOD PRES- SURE	PHYSICAL EXAMINATION
32	F	63	148	0	0	0	0	-	81	13	0	0	116/72	Negative
26	F	64	138	0	0	0	0	-	98	11	0	0	118/76	Negative
23	F	64	150	0	0	0	0	-	73	13	0	- 4%	108/80	Negative
23	F	67	146	0	0	0	0	-	78	12	0	- 7%	116/70	Negative
24	F	63	135	0	0	0	0	-	86	14	0	- 3%	110/74	Negative
23	F	62	132	0	0	0	0	-	82	6	0	- 9%	116/74	Negative
18	F	68	133	0	0	0	0	-	96	12	0	0	100/70	Soft syst lic basal murmur
21	F	60	117	0	0	0	0	-	82	10	0	-12%	110/78	Soft systolic basal murmur
32	M	69	148	0	0	0	0	-	98	2	0	-16%	108/75	Negative
23	M	68	135	0	0	0	0	-	90	11	0	- 4%	110/75	Negative
24	M	69	140	0	0	0	0	-	104	4	0	- 9%	120/80	Negative

*Erythrocyte sedimentation rate determined by modified Outler method; normal for men: 0 to 10; for women, 0 to 15.

†Percentage of heart size deviation from average normal according to Ungarleider tables.

lying down on a padded wooden table. Occasionally, when abnormalities were observed, the electrocardiogram was repeated in the erect position. Particular care was taken in the recording and development of the tracings, and most of this was done by the author. All of the subjects were adults between the ages of 18 and 35 years. There were 200 Negro men, 100 Negro women, 100 white men, and 100 white women. They were picked from the normal active personnel of an Army post, and no hospital patients were included. No one was included who had had a recent illness, a history of gonorrhea or syphilitic infection, or any complaints referable to the cardiovascular system. All subjects were told about the study in a general way and were reassured before the electrocardiograms were made. Each was rested for ten minutes to one hour. When asked to return for additional studies, they were once more assured that no heart disease was present and that they had no cause for concern.

Routine four-lead electrocardiograms (Leads I, II, III, and IV F) were made and examined. All subjects who showed any degree of T_4 inversion were requested to return for further testing. At this time, a careful history was obtained with particular reference to rheumatic fever, scarlet fever, recent pharyngitis, cardiovascular symptoms, and the use of any drugs. The temperature, weight, and height were recorded. The blood pressure was measured, and the heart was carefully examined. The following additional studies were obtained: (1) teleroentgenogram of the chest, (2) hemoglobin, (3) Kahn reaction, (4) examination of the blood film for sickling, and (5) sedimentation rate. Another electrocardiogram was then made, employing, in addition to the original four leads, the six standard precordial leads with the indifferent electrode on the left leg. In some cases Leads IV R, IV L, and IV V were also recorded.

Table I summarizes the physical descriptions and laboratory findings in those subjects who showed T-wave abnormalities and were studied sufficiently to be included. Three subjects were omitted from this list because of incomplete records.

RESULTS

The results of this study are summarized in Table II. It will be noted that, of the 300 Negroes studied, 4.6 per cent had tracings which would be considered abnormal. The women had a much larger incidence of T-wave abnormality: 4 per cent were diphasic, and 4 per cent were inverted. All of the abnormal tracings obtained from the women are reproduced in Figs. 1 and 2. The incidence of T-wave changes in the precordial leads of Negro men was 3 per cent while 1 per cent had frankly abnormal curves. The latter are reproduced in Figs. 3 and 4; those showing merely diphasic T waves are not shown. An electrocardiogram was obtained from one white man in which the T waves in the precordial leads were diphasic with the negative portion 0.5 mm. in depth. There were no abnormal tracings among the white women.

Table III is a summarized analysis of the records. Since it is not apparent from the tracings shown, it is well to add that the heart rates varied between 64 and 90 and there were no instances of abnormal arrhythmia. Several general impressions are possible from examination of the electrocardiograms. There

were no instances of abnormality of any portions of the curves derived from the limb leads. The axis varied between +33 and +103, i. e., normal to very slight right axis deviation; no instance of left axis deviation was noted. T₁ and T₂ were always upright and an inverse relationship apparently existed between T₂ and T₄; the greater the height of T₂, the greater the depth of T₄. T₃ was never frankly inverted but was flat in two instances and diphasic in one. All of the precordial T waves were diphasic or negative from Lead CF₁ through Lead CF₄; Leads CF₁ and CF₂ usually had the greatest negativity and Lead CF₄ had the least. In some instances, inversion was present in Lead CF₅ and even in CF₆, but, for the most part, the T waves in Leads CF₅ and CF₆ were upright. Where Lead CR (IV R) was made, the T waves were usually but not invariably upright. Leads IV L and IV V were variable.

TABLE II. SUMMARY OF THE FREQUENCY OF ABNORMAL PRECORDIAL T WAVES IN 300 ADULT NEGRO AND 200 WHITE SUBJECTS

Negro, both sexes (300)			
Normal curves.....	286	95.34%
Diphasic T ₄	8	2.66%
Inverted T ₄	6	2.00%
Negro men (200)			
Normal curves.....	194		
Diphasic T ₄	4		
Inverted T ₄	2		
Negro Women (100)			
Normal curves.....	92		
Diphasic T ₄	4		
Inverted T ₄	4		
Whites, both sexes (200)			
Normal curves.....	199	99.5%
Diphasic T ₄	1	00.5%
Inverted T ₄	0	00.0%
White men (100)			
Normal curves.....	99		
Diphasic T ₄	1		
White Women (100)			
Normal curves.....	100		

Approximately two months after the original tracings were obtained, those subjects who exhibited electrocardiographic abnormalities were requested to return for additional studies. All of the women and four of the men were reached, but the remainder had left the post and could not be re-examined. Of the electrocardiograms which were reported, six remained unchanged (*B* and *C* in Fig. 1, *G* and *H* in Fig. 2, Fig. 3, and one electrocardiogram not shown). *A* in Fig. 1 had become entirely normal. *D* retained an inverted T wave in Lead CF₂ but the T wave in Lead CF₃ had become diphasic and that in Lead CF₄ had become upright. In *E*, the T wave in Lead CF₅ became upright and in Leads CF₃ and CF₄ it was diphasic with Lead CF₂ unchanged. In *F*, the T wave in Lead CF₄ became positive, in Lead CF₃ it became flat, and in Lead CF₂ there was no change. One of the tracings, that of a Negro man, which demonstrated diphasic T waves, became

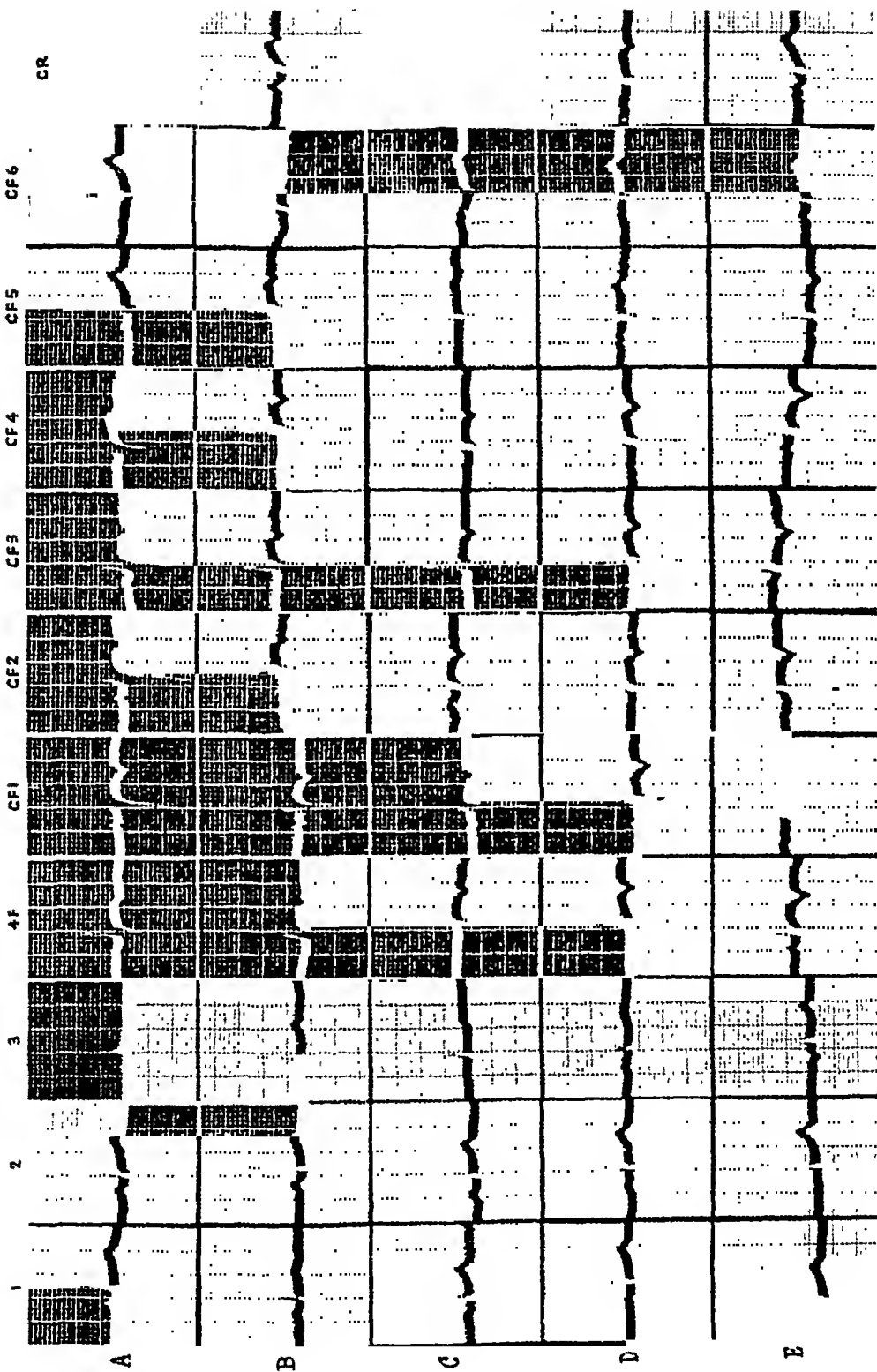


Fig. 1.—Abnormal electrocardiograms of five Negro women.

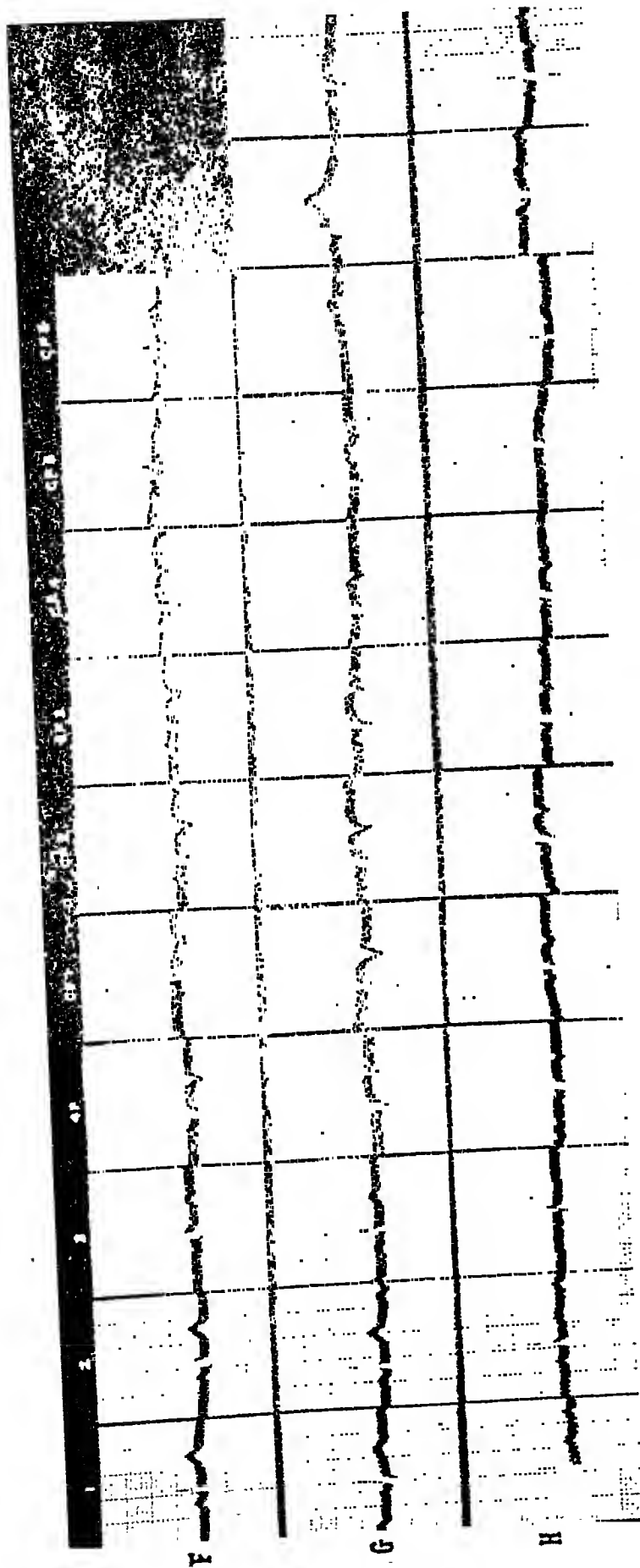


Fig. 2.—Abnormal electrocardiograms of three Negro women.

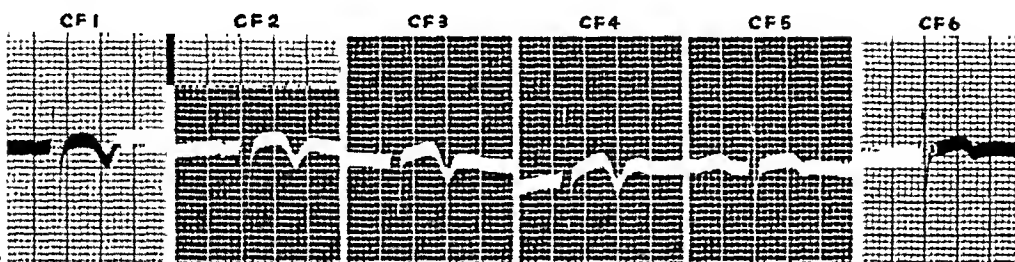
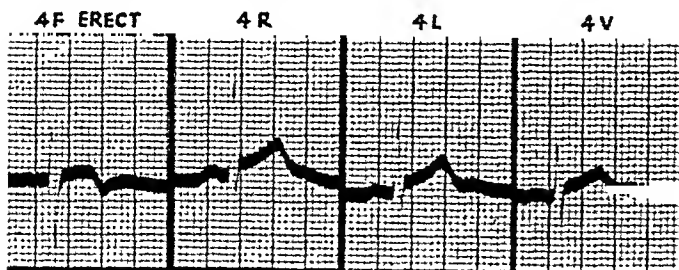
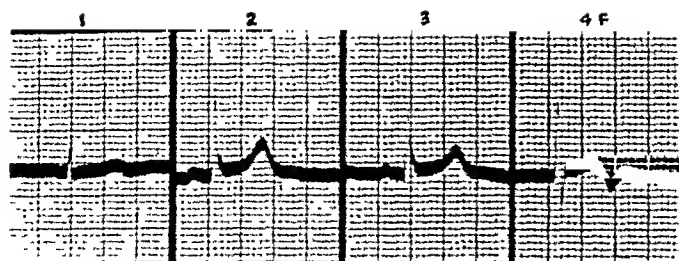


Fig. 3.—Abnormal electrocardiograms of a Negro man.

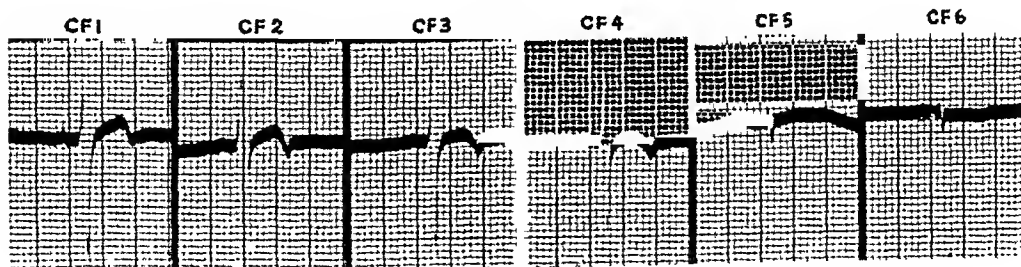
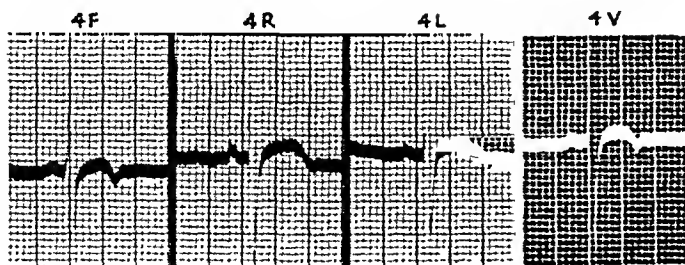
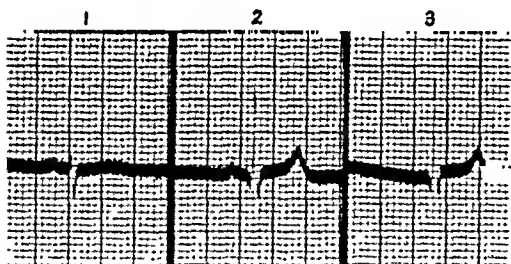


Fig. 4.—Abnormal electrocardiogram of a Negro man.

TABLE III. SUMMARY OF RECORD ANALYSIS*

RECORD DESIGNATION	P-R INTERVAL	QRS DURATION	AXIS	T ₁	T ₂	T ₃	T ₄ (IV F)	T-CF ₁	T-CF ₂	T-CF ₃	T-CF ₄	T-CF ₅	-CF ₆	T-IV R	T-IV L
A.....	0.14	0.09	+37	+1.	+1.5	0.0	+1.0 -1.0	-2.0	-1.5	-1.8	+2.0 -0.5	+3.0	+2.5		
B.....	0.14	0.08	+73	+0.5	+1.5	+1.0	+1.2 -0.5	-1.5	+1.0 -0.5	+1.0 -1.0	+1.0 -1.5	+0.5 -0.5	+0.5	+1.0 -1.0	
C.....	0.18	0.06	+43	+2.0	+2.0	0.0	-1.5	-2.0	-1.5	-1.0	-1.0	+0.5	+1.5		
D.....	0.18	0.08	+33	+1.5	+0.2	+0.5	+0.5 -1.5	-3.0	-2.0	-2.0	-2.0	+1.5	+2.0	+0.5 -1.5	
E.....	0.11	0.06	+62	+1.5	+3.0	+1.5	-3.0	-2.5	-2.5	-2.5	-3.3	-1.5	+1.5	+2.2	
F.....	0.12	0.10	+58	+2.0	+2.3	+0.5	-1.6	-1.5	-2.0	-1.4	+0.5	+0.5	+1.5		
G.....	0.15	0.06	+47	+1.5	+2.5	+1.0	+0.5	-3.0	-3.0	-1.9	+0.5	+1.0	+1.3	+3.0	-0.5
H.....	0.14	0.08	+34	+1.0	+0.5	-0.3	-1.0	-1.2	-1.0	-1.0	-1.0	+0.5	+0.5	+1.0 -0.5	-1.0
Fig. 3.....	0.14	0.09	+87	+0.1	+4.0	+3.0	-3.0	-3.0	-3.5	-3.0	-3.0	+1.0 -0.5	+1.0 -0.5	+3.0	+3.0
Fig. 4.....	0.12	0.09	+103	+0.5	+3.5	+3.0	-2.0	+2.0 -0.5	+1.0 -1.0	-1.5	-1.5	+1.0	0.0	+2.0	+1.0

*T-wave height expressed in millimeters.

entirely normal while another developed frankly inverted T waves. It would appear, therefore, that when changes in the direction of normal become manifest they do so first in those leads farthest from the sternum. In addition, it is probable that changes may occur either toward or away from the normal pattern.

DISCUSSION

The size of the group being studied is too small for detailed statistical conclusions. However, certain facts are evident. T wave inversion in the precordial leads is far more common among normal adult Negroes than among white subjects and is apparently more frequent in Negro women than in Negro men. In no case here reported was there any cardiovascular complaint or any demonstrable evidence of organic or functional disease of the heart. None of the subjects had any active or recent infection. The abnormalities were noted in a group of healthy, confident, young men and women who had not been smoking, taking drugs, drinking cold water, or hyperventilating.

In a general way, it is noted that in the cases reported in this study, the heart tended to be relatively small and there were no instances of enlargement. Similarly, the electrical axis fell toward the right and was never rotated to the left. Although a few of the women were rather stout, none was obese and most of the chests were thin. The men, particularly, were thin chested. These observations tend to confirm the impression of juvenile chest configuration in these individuals.

In the literature reviewed it is probable that the studies were carried out on white subjects. References to electrocardiographic studies on the Negro are limited. Laws,²⁰ in a discussion of the etiology of heart disease in the Negro, concludes that "The Negro develops heart disease at an earlier age, on the average, than the white." Is it likely that the Negro subjects under discussion were demonstrating the first evidence of organic heart disease? Observations incident to the present study argue against such a conclusion. It is also thought that certain degenerative cardiac conditions, angina pectoris, for example, occur less frequently in Negro than in white subjects. Weiss²¹ has reported, however, that angina in Negroes is fairly common. Ashman,²² who made an electrocardiographic study of Caucasians and Negroes, reported no unusual incidence of T-wave abnormality. Furthermore, all of his subjects were over 30 years of age and the data were obtained from hospital records. Presumably, these were all cardiac patients since there was a high incidence of organic heart disease.

Apparent inadequacies of the literature are noted. At the present time, no comparative studies can be found on white and Negro children. It is known that most white children have acquired an upright T wave in the chest lead by the age of 15 years. Can the same be said about the Negro? Comparatively few studies have been recorded regarding the manner in which the T wave becomes upright during adolescence. Does it become positive first in the fifth or sixth precordial position, as seems probable, or are the changes first apparent in other positions? Is the progress from the negative to the positive direction

constant and steady, or is it subject to frequent recessions? The work of Robinson and his associates¹⁰ suggests that the latter is actually the case.

It is possible that not all cases of T_4 inversion in the group herein reported were due to the same cause. It will be recalled that of 12 subjects who were re-examined after approximately ten weeks, five showed changes toward the normal. It would be altogether too fortuitous to expect that so high a proportion should have chosen the same time to acquire adult characteristics. However, since it is uncertain that the erection of a juvenile T wave is a continuous progression and not an unsteady equilibrium, that possibility must be considered. Unfortunately, because of the constantly changing character of the personnel on an Army post, it was not possible to repeat the studies on the same group.

There exists, therefore, an apparent abnormality, possibly transient or shifting in character, in a very appreciable percentage of young and presumably healthy Negro men and women. It is more common in women than in men and apparently occurs very rarely in white subjects. It is associated with suggestive juvenile characteristics. Women's chests are normally less broad from side to side than men's and this may account for the higher incidence observed in the female sex.

These findings were noted in the complete absence of symptoms or signs of organic or functional heart disease. In a similar manner, there was no evidence of current or recent infection, rheumatic fever, drugs, syphilis, anemia, or sickling of erythrocytes. The reasons noted and the exclusion of other known causes of such anomalies lead to the conclusion that the T-wave inversion in the chest leads of otherwise normal adults constitutes a persistence of the juvenile pattern and should be considered a normal variant.

Since this anomaly is manifested more frequently when the left leg rather than the right arm is employed for the indifferent electrode, it is desirable that the study be repeated using various indifferent connections. Electrocardiograms should also be made over a prolonged period of time, as the phenomenon apparently disappears with the passage of time.

Much additional study of the electrocardiograms of youthful white and Negro subjects will be required before a satisfactory explanation of this apparent anomaly can be made. At the present time, there seems to be no adequate reason for the greater frequency of juvenile electrocardiograms in adult Negroes than in adult white subjects.

SUMMARY

1. In an electrocardiographic survey of 500 healthy adults, 300 Negro and 200 white subjects, diphasic or inverted T waves in the precordial leads were observed in 14 Negroes; eight among 100 women and six among 200 men. Among white subjects a diphasic T wave was noted in only one instance.

2. It is suggested that the presence of diphasic or inverted T waves in the precordial leads under the circumstances constituted a persistence of the juvenile pattern and was not a manifestation of organic heart disease.

REFERENCES

1. Joint Recommendations of the American Heart Association and Cardiac Society of Great Britain and Ireland. Standardization of Precordial Leads, *AM. HEART J.* 15: 107, 1938.
2. Shipley, R. A., and Halloran, W. R.: The Four Lead Electrocardiogram in 200 Normal Men and Women, *AM. HEART J.* 11: 325, 1936.
3. Skulassen, T. and Larsen, K.: The Normal Electrocardiogram, *AM. HEART J.* 22: 645, 1941.
4. Wood, C. F., Wolferth, C. C., and Miller, T. G.: Electrocardiography in Military Medicine With Special Reference to Its Lack of Value in the Study of Recruits, *War Med.* 1: 696, 1941.
5. Graybiel, A., McFarland, R. A., Gates, D. C., and Webster, F. A.: Analysis of the Electrocardiograms Obtained From 1,000 Young Healthy Aviators, *AM. HEART J.* 27: 524, 1944.
6. Rosenblum, H., and Sampson, J. K.: The Study of Lead IV of the Electrocardiogram in Children With Special Reference to the Direction of the Excursion of the T Wave, *AM. HEART J.* 11: 49, 1936.
7. Dwan, P. F., and Shapiro, W. J.: The Four Lead Electrocardiogram of Children, *Am. J. Dis. Child.* 54: 265, 1937.
8. Deeds, D., and Barnes, A. R.: The Characteristics of the Chest Lead Electrocardiograms of 100 Normal Adults, *AM. HEART J.* 20: 261, 1940.
9. Master, A. M., Dack, S., and Jaffe, H. L.: The Precordiogram of Normal Children, *Am. J. Dis. Child.* 53: 1000, 1937.
10. Robinow, M., Katz, L. N., and Bolning, A.: The Appearance of the T-Wave in Lead IV in Normal Children and in Children With Rheumatic Heart Disease, *AM. HEART J.* 12: 88, 1936.
11. Edeiken, J., Wolferth, C. C., and Wood, F. C.: The Significance of an Upright or Diphasic T-Wave in Lead IV When It Is the Only Definite Abnormality of the Adult Electrocardiogram, *AM. HEART J.* 12: 666, 1936.
12. Sodeman, W. A.: The Occurrence of an Upright T-Wave in Lead IV in a Patient Without Other Evidence of Heart Disease, *AM. HEART J.* 14: 367, 1937.
13. Shanno, R. L.: Variations in Normal Precordial Electrocardiograms. A Report of Observation on 100 Normal Subjects, *AM. HEART J.* 19: 713, 1940.
14. Pardee, H. L.: Electrocardiograms With Normal Limb Leads and With Abnormality in Only One of Four Precordial Leads. *J. Mt. Sinai Hosp.* 8: 898, 1942.
15. Dupuy, H.: Normal Variations of the T-Wave Seen Among Army Soldiers, *New Orleans M. & S. J.* 96: 239, 1943.
16. Thompson, P.: The Electrocardiogram in the Hyperventilation Syndrome, *AM. HEART J.* 25: 372, 1943.
17. Katz, L. N.: Lecture Before American College of Physicians, November, 1944.
18. McGuire, J.: Personal communication.
19. Graybiel, A., Starr, R. S., and White, P. D.: Electrocardiographic Changes Following Inhalation of Tobacco Smoke, *AM. HEART J.* 15: 89, 1938.
20. Laws, C. L.: The Etiology of Heart Disease in Whites and Negroes in Tennessee, *AM. HEART J.* 8: 608, 1933.
21. Weiss, M. M.: The Problem of Angina Pectoris in the Negro, *AM. HEART J.* 17: 711, 1939.
22. Ashman, R.: An Electrocardiographic Study of Caucasians and Negroes, *Tri-State M. J.* 13: 2686, 1941.

ELECTROCARDIOGRAPHIC CHANGES OCCURRING DURING UPPER RESPIRATORY INFECTIONS

MAJOR DENNISON YOUNG, MEDICAL CORPS, ARMY OF THE UNITED STATES

IT IS becoming increasingly apparent that transient or permanent cardiac involvement as a result of a toxic state or direct bacterial or viral invasion may be a concomitant of many infectious diseases.¹⁻⁴ The following report is presented to demonstrate cardiac susceptibility in the course of mild, apparently benign upper respiratory infection, in many instances with no bacteriologic evidence of pathogenic microorganisms in the nasopharyngeal secretions.

MATERIAL AND METHODS

The thirteen patients presented in this series were all military personnel, hospitalized because of respiratory infection. Cultures were made routinely from swabbings of the nasopharynx. Serial electrocardiograms at two- or three-day intervals, usually starting on the day after admission, and repeated cardiac fluoroscopic and clinical examinations were made.

RESULTS

The clinical and laboratory data are shown in Table I. Of the thirteen cases, Group A beta hemolytic streptococci were present in nasopharyngeal cultures in only five. Only one type was recovered on repeated culture from each of these five cases. In one case a Group B and in one a Group G beta hemolytic streptococcus was isolated. In six cases, a beta hemolytic streptococcus was at no time discovered in the nasopharynx, repeated cultures showing only the usual nasopharyngeal organisms.

The most frequent electrocardiographic changes obtained were T-wave inversions and depressions. These occurred as the only change in seven cases. Four patients developed auriculoventricular conduction disturbances with prolongation of the P-R interval from 0.04 to 0.05 second beyond the normal duration. One additional patient showed marked T-wave changes and an intermittent A-V nodal rhythm. One patient also showed a widening of the QRS complex and runs of A-V nodal tachycardia. T-wave changes and the variation of the P-R interval cannot be ascribed to postural effects, for all electrocardiograms were taken with the patients in the recumbent position.

Clinically, except for Case 5, these patients were not acutely ill on admission nor during their period of hospitalization. There was no essential difference in the severity or duration of the acute phase between those with a hemolytic

TABLE I. CLINICAL AND LABORATORY DATA ON THIRTEEN CASES OF UPPER RESPIRATORY INFECTION

CASE	AGE	DIAGNOSIS	ECG CHANGE (T WAVES IN MM.; P-R AND QRS IN SEC.)	DAYS IN- FECTION PRESENT BEFORE ECG CHANGE	DURATION OF ECG CHANGE (DAYS)	THROAT CULTURE (BETA HEMO- LYTIC STREPTO- COCCUS)	OTHER LABORATORY DATA		REMARKS
							WHITE BLOOD CELLS††	ERYTHROCYTE SEDIMENTA- TION RATE (WESTERGEN)	
1	21	Acute tonsillitis	T ₁ , +1.0 to +1.5 T ₂ , +1.0 to +2.0 T ₃ , Semi-inverted to +1	19	10	0	10,200, P 84	1 mm.	First admission
		Acute tonsillitis	T ₁ , +0.5 to +1.2 to +1.2 T ₂ , +0.5 to -1.5 to +1.0 T ₃ , -1.0 to -2.0 to semi-inv. T ₄ , +2.0 to 0.0 to +3.5	5	41	Group A —not typable	19,000, P 88	81 mm.	Second admission, 5 months later; re- ceived 15 Gm. sul- fadiazine
2	20	Acute tonsillitis	P-R, 0.21 to 0.16	11	9	0	9,950, P 61	50 mm.	
3	23	Acute nasopharyngitis	T ₁ , +1.0 to 0.0 T ₄ , +2.2 to -1.0	5	83	0	5,100, P 53	6 mm.	
4	19	Acute nasopharyngitis	P-R, 0.20 to 0.16	3	7	0	5,000, P 54	18 mm.	
5	28	Acute tonsillitis	T ₁ , +3.0 to +3.5 T ₂ , +1.5 to -1.3 T ₃ , -3.0 to -3.5 T ₄ , +8.5 to 13.5	28	74	Group A, Type 12	19,500, P 90	28 mm.	Received 54 Gm. sul- fadiazine
6	32	Acute tonsillitis	T ₁ , 0.0 to +1.0 T ₂ , -1.0 to +0.5 T ₃ , -2.0 to -1.0 T ₄ , +2.0 to +2.5 Intermittent A-V nodal rhythm	8	72	Group B	6,300, P 71	46 mm.	Received 20 Gm. sul- fadiazine

7	25	Acute tonsillitis	T ₁ , +0.5 to +2.0 T ₂ , +0.5 to +1.5 T ₃ , 0.0 to +0.5 T ₄ , +0.5 to +2.5	8	10	Group A, Type 41	15,200, P 92		Received 15 Gm. sul- fadiazine
8	29	Acute nasopharyngitis	QRS, 0.12 to 0.10 Runs of A-V nodal tachycardia	6	24	0	6,100, P 63		
9	18	Acute tonsillitis	T ₁ , +1.0 to +2.0 T ₂ , +1.5 to +2.7 T ₃ , -2.0 to +3.0	10	8	Group G	5,600, P. 53	3 mm.	
10	23	Infectious mono- nucleosis	P-R, 0.16 to 0.20	26	12	Group A, Type 12	8,200, L 54 (many atypical)	22 mm.	Heterophile, +1:3584
11	21	Acute nasopharyngitis	P-R, 0.22 to 0.17	3	5	0	4,200, P 64		
12	20	Acute nasopharyngitis	T ₁ , Semi-inverted to +2.5 T ₂ , +2.5 to +2.7 T ₃ , +2.5 to +1.0 T ₄ , +2.5 to +8.0	5	7	0	5,600, P 70	12 mm.	
13	20	Infectious mono- nucleosis	T ₁ , +0.5 to +1.0 T ₂ , +1.5 to +3.0 T ₃ , +0.8 to +2.0 T ₄ , +1.0 to +3.0	6	12	Group A, Type 36	6,300, L 74 (one-third atypical)	10 mm.	Heterophile, +1:56; received 78 Gm. sulfadiazine

*Polymorphonuclears.

†Lymphocytes.

streptococcal infection of the throat and those with a simple nasopharyngitis. A leucocytosis was present in three of the patients with Group A infection but in none of the others. The erythrocyte sedimentation rate was not elevated in all cases. Two of the patients with Group A hemolytic streptococci in the nasopharynx clinically and hematologically had infectious mononucleosis.

None of these patients had a past history suggestive of rheumatic fever. None showed clinical or fluoroscopic evidence of pre-existing cardiac disease nor did they develop any clinical signs or symptoms of heart disease, other than the electrocardiographic changes, during the period of observation. There was no laboratory evidence of a renewed active infectious process during the period that electrocardiographic changes were present.

Only one patient developed clinical manifestations suggesting rheumatic fever (Case 10). This patient suffered from fairly severe arthralgias for one week during his illness, but there were no objective signs of joint involvement. He had a typical infectious mononucleosis with a heterophile agglutination titer of 1:3,584.

In a fruitless attempt to eliminate the hemolytic streptococcus from the nasopharynx, five patients in this series (Table I, Cases 1, 5, 6, 7, and 13) were given sulfadiazine in varying doses. In these five the drug was started two, twenty-eight, one, four, and ten days, respectively, prior to the first electrocardiographic indication of myocardial involvement. All other patients received only symptomatic treatment during the acute phase.

CASE REPORTS

CASE 1.—This case is of considerable interest in that the patient was hospitalized twice with acute tonsillitis and on each admission developed electrocardiographic changes despite a distinct difference in the nasopharyngeal cultures. The first admission was because of a progressively severe sore throat of one week's duration. The oral temperature was 101° F. and examination revealed diffuse injection of the pharynx; the tonsils were large and inflamed. The throat culture showed no unusual organisms. Treatment was entirely symptomatic. Signs and symptoms rapidly subsided and the temperature returned to normal on the fifth hospital day. Electrocardiographic evidence of myocardial involvement, manifested by low T waves in Leads I and II and inversion of the T wave in Lead III, appeared on the nineteenth day of illness. Three days later the tracing had returned to normal (Fig. 1, *A* and *B*).

The patient was well at time of discharge from the hospital and remained so until five months later when he was readmitted because of sore throat, malaise, and fever of one day's duration. The tonsils were large, reddened, and covered with exudate. The oral temperature was 103° F. and remained elevated for the first four hospital days. Throat culture revealed a Group A beta hemolytic streptococcus which was not typable. On the fifth day of illness, significant changes were present in the T waves of the electrocardiogram. These changes became progressively more marked, and the tracing did not return to normal until forty-one days later (Fig. 1, *C*, *D*, and *E*). During this period the patient was objectively and subjectively well; laboratory data revealed no evidence of infection after the tonsillitis had subsided. Subsequent follow-up for two months after discharge from the hospital revealed no clinical or laboratory abnormalities.

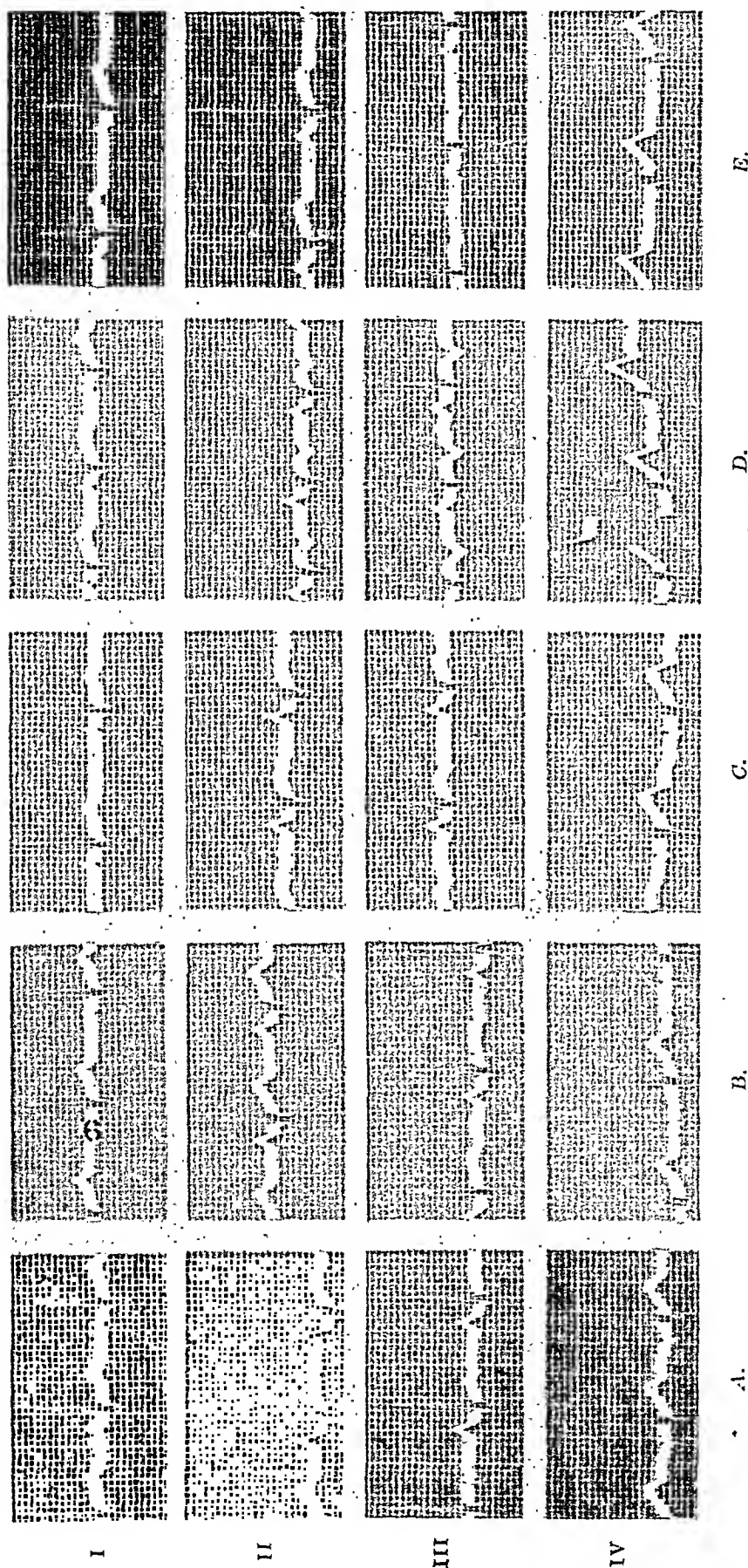


Fig. 1.—Case 1. Electrocardiograms A and B taken nineteen and twenty-two days, respectively, after onset of acute tonsillitis. C, D, and E taken five, twelve, and forty-one days, respectively, after onset of similar illness five months later.

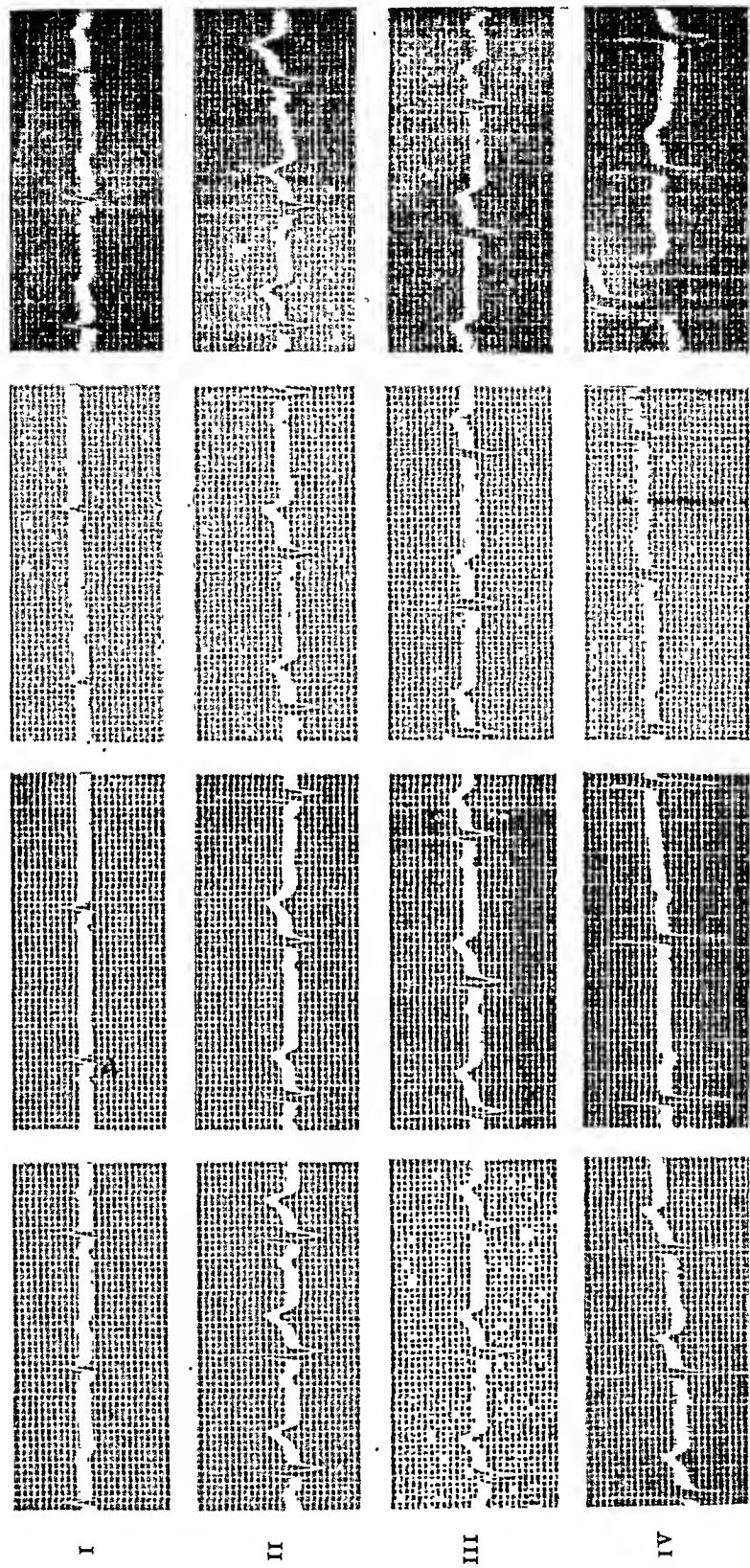


Fig. 2.—Case 3. Electrocardiograms A, B, C, and D taken two, five, twenty, and eighty-three days, respectively, after onset of acute nasopharyngitis.

Two other cases illustrating the development of marked electrocardiographic changes early in the course of simple upper respiratory infections are presented.

CASE 3.—W. C. was hospitalized because of cough, fever, and chilliness of two days' duration. The temperature was 100° F. orally on admission, and although the patient appeared moderately ill, the only abnormal finding was congestion of the nasal mucosa. Laboratory data were normal. Repeated nasopharyngeal cultures failed to show any unusual organisms. The patient was afebrile after the first hospital day and all signs and symptoms were gone in four days. At no time was there a leucocytosis or elevation of the erythrocyte sedimentation rate. During a five-month period of observation he displayed no clinical cardiovascular signs or symptoms.

The electrocardiogram on the fifth day of illness revealed an almost isoelectric T wave in Lead I and an inverted T wave in Lead IV (Fig. 2, *A* and *B*). Twenty days later T_1 measured 1 mm. and T_4 was slightly upright (Fig. 2, *C*). The first normal tracing was obtained eighty-three days after the onset of the upper respiratory infection (Fig. 2, *D*); subsequent electrocardiograms showed no further change.

CASE 9.—S. C., an 18-year-old soldier, was admitted to the hospital because of a slight non-productive cough and sore throat of three days' duration. Examination revealed moderate swelling and redness of the tonsils with flecks of white exudate on the surface. The patient was not acutely ill and was afebrile on admission and remained so throughout his hospital stay. The acute manifestations subsided in three days.

Laboratory data were normal and did not change significantly during the period of hospitalization. A Group G beta hemolytic streptococcus was obtained on initial throat culture and was present on repeated nasopharyngeal swabbings. No other beta hemolytic streptococci were obtained.

The electrocardiogram taken ten days after the onset of the patient's upper respiratory infection showed a deeply inverted T wave in the fourth lead. Two days later T_4 was upright but the T waves in the first three leads were distinctly lower. One week later the T waves were normal in all leads and subsequent follow-up studies revealed no change (Fig. 3, *A*, *B*, and *C*).

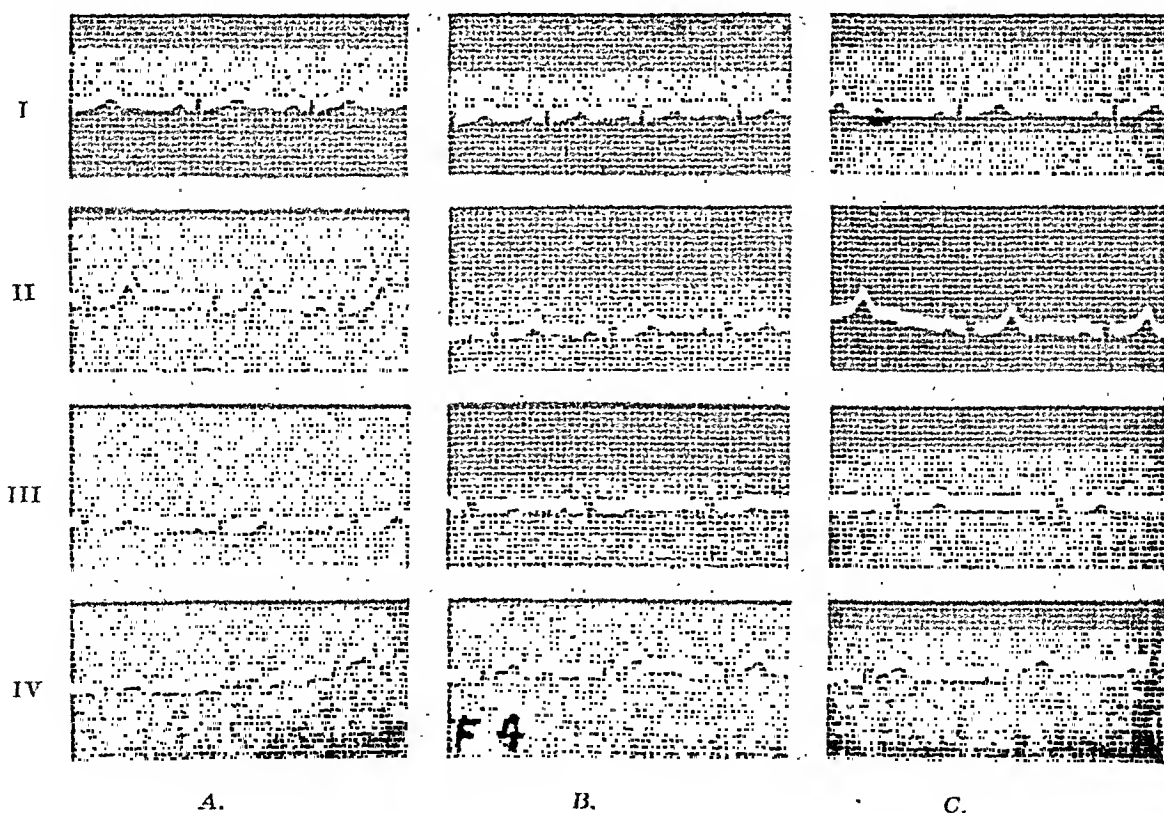


Fig. 3.—Case 9. Electrocardiograms *A*, *B*, and *C* taken ten, twelve, and nineteen days, respectively, after onset of acute tonsillitis.

DISCUSSION

The electrocardiographic changes found in these thirteen patients are unequivocal evidence of myocardial involvement. Since all patients recovered, the exact pathologic significance of the electrocardiographic changes can only be surmised. Candel and Wheelock³ recently reported a case of sudden death in a patient with acute suppurative tonsillitis from whom throat cultures had shown a beta hemolytic streptococcus (not grouped). Microscopically the myocardium showed pronounced fragmentation of the bundles with loss of cross striations, disintegration of muscle nuclei, interstitial edema, and a widespread diffuse infiltration of the interstitial tissue by polymorphonuclear cells. This apparently is the first recorded post-mortem report of acute nonspecific myocarditis following acute tonsillitis, although Schultz,⁵ in 1937, recorded a case of sudden death in a 21-year-old soldier in whom autopsy revealed a diffuse interstitial myocarditis believed to have been secondary to tonsillar infection.

Several authors have reported electrocardiographic evidence of acute myocarditis following tonsillitis. Scherf⁶ demonstrated five such cases and indicated that from 10 to 15 per cent of patients with acute tonsillitis develop signs, symptoms, or changes in the electrocardiogram suggesting myocardial involvement. Carr and Walsh⁷ and Maher and Wosika⁸ have also recorded electrocardiographic changes with tonsillar infection. In their paper on acute nonspecific myocarditis, Candel and Wheelock³ included a case of peritonsillar abscess and one of infectious mononucleosis.

It is quite possible that electrocardiographic changes occur in much greater frequency in all respiratory infections than has been previously recognized. Scherf and Boyd⁹ suggest that with the frequency of infectious diseases and miscellaneous infections such as tonsillitis, there are but few individuals who at some time do not have small inflammatory myocardial foci. To date, however, since no serial electrocardiographic study has been made in a large series of patients with upper respiratory infection, an accurate statistical incidence of evidence of cardiac involvement in this type of illness has not been obtained.

Unfortunately the bacteriologic findings in the nasopharynx were not correlated with the evidence of myocardial involvement in previously reported cases. This may be of extreme importance in an attempt to evaluate the immediate significance of the electrocardiographic changes as well as the future outlook for the patient in view of the opinion recently expressed by Rantz, Boisvert, and Spink.¹⁰

These authors obtained electrocardiographic evidence of carditis similar to that described here in 10.8 per cent (twenty cases) of 185 patients on whom serial electrocardiograms were taken during and following Group A beta hemolytic streptococcal throat infections. A true latent period between recovery from the sore throat and the development of changes in the electrocardiogram occurred in only six of these patients. When a latent period was demonstrated, reinfection by a new type of Group A streptococcus had frequently taken place.

Because carditis was not demonstrable in 80 per cent of their series, a toxic etiology for the carditis in the group with no latent period was rejected. Pre-

viously unrecognized streptococcic respiratory infection with the establishment of an abnormal tissue sensitivity was postulated as the mechanism for the pathogenesis of the myocardial involvement in these patients. In those patients in whom a latent period between the respiratory infection and carditis occurred, the same mechanism was considered responsible because a new type of Group A streptococcus was discovered in the throat on subsequent cultures. Thus these authors suggested grouping cases of carditis with and without a latent period following the acute respiratory phase, rheumatic fever, and postscarlatinal arthritis under the term "poststreptococcic state."

If one is inclined to accept this attractive hypothesis, then the electrocardiographic changes demonstrated at least in some of the thirteen patients in the present study assume an even greater potential significance. Five of these patients repeatedly showed a Group A hemolytic streptococcus in the nasopharynx during the acute phase and during convalescence. Of these five, two patients had definite infectious mononucleosis. Although a study previously carried out at this hospital demonstrated a Group A carrier rate of only 1.9 per cent in this geographic area¹¹ it is quite possible that the organisms were not responsible for the disease process in the two patients with infectious mononucleosis and that they were merely carriers of the hemolytic streptococcus. A Group B hemolytic streptococcus was isolated in one case. This organism is not infrequently found in the upper respiratory tract and is usually not pathogenic for man. In one case a Group G streptococcus was repeatedly isolated. This type may at times be of clinical significance.

Granting that five and possibly seven cases were actually infected with hemolytic streptococci, it is to be noted that comparable electrocardiographic changes occurred in six patients from whose throats at no time unusual organisms were isolated. This certainly suggests a nonspecific toxic process as the causative mechanism and can just as readily be applied to those cases in which pathogenic organisms were demonstrated as can the theory of specific sensitization of the myocardium by products of the hemolytic streptococcus.

In regard to the "streptococcal group" of cases, and perhaps even in the others, the mechanism of the production of carditis is of more than academic importance. Neither the study by Rantz, Boisvert, and Spink¹⁰ nor this study reveals the eventual outcome in such patients. It is well known that signs of valvular disease may not appear for a considerable period of time after all evidence of rheumatic fever has subsided. Many studies have also shown that in from 25 to 50 per cent of patients in whom rheumatic heart disease is found, no antecedent history of rheumatic fever can be obtained. Thus, if such patients who demonstrate evidence of carditis during respiratory infection without other accepted criteria of rheumatic fever¹² are considered to be in the same group as those with the "rheumatic state," then prognosis in such patients must be guarded, and certainly every effort must be made to prevent recurrent respiratory infection in such individuals. If, on the other hand, the underlying mechanism is considered to be of nonspecific "toxic" origin and not related to a "rheumatic" sensitization of cardiac tissue, then the possibility of progressive or future cardiac

damage is considerably reduced and electrocardiographic changes assume much less importance.

Upper respiratory infection has been at times cited as the cause of Fiedler's or diffuse isolated myocarditis.¹ Hansmann and Schenken¹³ suggest that the microscopic appearance of the muscle fibers in isolated myocarditis makes one suspect that the same thing occurs in the milder forms of toxic myocarditis from which patients usually recover without clinical recognition. Thus transient electrocardiographic changes occurring in upper respiratory infections would be considered to represent a *forme fruste* of acute diffuse myocarditis.

Candel and Wheelock³ suggest this same possibility in discussing acute myocarditis following tonsillitis. They also speak of permanent abnormal electrocardiographic alteration. However, it would seem that in view of changes in four of our cases persisting for forty-one, eighty-three, seventy-four, and seventy-two days, respectively, before returning to normal, it is dangerous to conclude without a long follow-up period that permanent changes have resulted.

While it is most likely that the electrocardiographic changes in those patients who received sulfadiazine in an attempt to eliminate the hemolytic streptococcus from the nasopharynx were due to the respiratory infection, in view of recent necropsy and experimental evidence of myocardial involvement due to sulfonamide administration,¹⁴⁻²² this drug cannot be entirely excluded as an etiologic factor. Electrocardiographic evidence of myocardial involvement due to sulfonamides alone has recently been obtained on six patients. This study will form the basis of a subsequent report. In this particular series, however, the drug may at best be considered an additive toxic factor rather than the sole responsible one for the electrocardiographic changes.

It is important to note that in none of these thirteen patients did cardiac signs or symptoms develop during the period when the electrocardiogram indicated myocardial involvement. This is in marked contrast with the experience of Scherf,⁶ who described weakness, palpitation, slight dyspnea, precordial or substernal pain, apprehension, tachycardia, and, in more severe cases, cardiac enlargement, gallop rhythm, and rarely congestive failure as occurring from one to two days after the onset of acute tonsillitis or shortly after the acute respiratory phase had subsided. The discrepancy between these two reports may possibly be attributed to the fact that our patients were all previously healthy individuals with greater cardiac reserve. It is apparent that on the basis of the clinical manifestations of the thirteen patients in this study, myocardial involvement would not have been suspected, so that the present report can offer no indications as to when or in which particular patients with upper respiratory infection serial electrocardiographic studies should be made.

SUMMARY AND CONCLUSIONS

1. Thirteen cases of upper respiratory infection in which electrocardiographic evidence of myocardial involvement was obtained are presented. Group A beta hemolytic streptococci were isolated on throat culture from only five of these thirteen patients.

2. The demonstration of comparable electrocardiographic changes in patients with and without hemolytic streptococcal respiratory infection favors a nonspecific toxic etiology as the underlying mechanism for both rather than the theory of streptococcal "rheumatic" sensitization of the myocardium.

3. Whether or not such cases represent a *forme fruste* of Fiedler's myocarditis can only be speculated upon, but this possibility is worthy of serious consideration.

4. The possible relation of sulfonamide administration to the development of myocardial changes in some of the patients is mentioned, but this may be at most an additive factor.

5. The absence of cardiovascular signs and symptoms in these patients is noted, so that no clinical indications for electrocardiographic study in patients with upper respiratory infection exist.

6. Present knowledge does not allow the inference that electrocardiograms should be taken routinely during upper respiratory infection.

REFERENCES

1. Saphir, O.: Myocarditis. A General Review With an Analysis of 240 Cases, Arch. Path. 32: 1000, 1941; 33: 88, 1942.
2. Finland, M., Parker, F., Jr., Barnes, M. W., and Jolliffe, L. S.: Acute Myocarditis in Influenza A Infections. Two Cases of Non-Bacterial Myocarditis With Isolation of Virus From the Lungs, Am. J. M. Sc. 209: 455, 1945.
3. Candel, S., and Wheelock, M. C.: Acute Non-Specific Myocarditis, Ann. Int. Med. 23: 309, 1945.
4. Editorial: Acute Non-Specific Myocarditis, J. A. M. A. 129: 1018, 1945.
5. Schultz: Quoted by Saphir.¹
6. Scherf, D.: Myocarditis Following Acute Tonsillitis, Bull. New York M. Coll. 3: 252, 1940.
7. Carr, J. G., and Walsh, J. A.: Acute Infectious Myocarditis, Illinois M. J. 65: 134, 1934.
8. Maher, C. C., and Wosika, P. H.: Electrocardiography, ed. 3, Baltimore, 1940, Williams & Wilkins Co., p. 297.
9. Scherf, D., and Boyd, L. J.: Cardiovascular Diseases, St. Louis, 1939, The C. V. Mosby Co., pp. 176-180.
10. Rantz, L. A., Boisvert, P. J., and Spink, W. W.: Etiology and Pathogenesis of Rheumatic Fever, Arch. Int. Med. 76: 131, 1945.
11. Glazer, A. M., and Gots, J. S.: The Incidence and Epidemiological Significance of Hemolytic Streptococci in a Florida Army Camp, South. M. J. 37: 628, 1944.
12. Jones, T. D.: The Diagnosis of Rheumatic Fever, J. A. M. A. 126: 481, 1944.
13. Hansmann, G. H., and Schenken, J. R.: Acute Isolated Myocarditis; Report of a Case With a Study of the Development of the Lesion, AM. HEART J. 15: 749, 1938.
14. Nelson, A. A.: Histopathological Changes in Hens and Rabbits Following Administration of Sulfanilamide and Sulfanilyl Sulfanilamide (di-sulfanilamide), Pub. Health Rep. 54: 106, 1939.
15. French, A. J., and Weller, C. V.: Interstitial Myocarditis Following the Clinical and Experimental Use of Sulfonamide Drugs, Am. J. Path. 18: 109, 1942.
16. Lederer, M., and Rosenblatt, P.: Death During Sulfathiazole Therapy: Pathology and Clinical Observations on Four Cases With Autopsy, J. A. M. A. 119: 8, 1942.
17. (a) Rich, A. R.: The Role of Hypersensitivity in Periarthritis Nodosa as Indicated by Seven Cases Developing During Serum Sickness and Sulfonamide Therapy, Bull. Johns Hopkins Hosp. 71: 123, 1942.
(b) Rich, A. R.: Additional Evidence of the Role of Hypersensitivity in the Etiology of Periarthritis Nodosa, Bull. Johns Hopkins Hosp. 71: 375, 1942.
18. Simon, M. A., and Kaufmann, M.: Death Following Sulfathiazole Therapy, Canad. M. A. J. 48: 23, 1943.
19. Rich, A. R., and Gregory, J. E.: Experimental Demonstration That Periarthritis Nodosa Is a Manifestation of Hypersensitivity, Bull. Johns Hopkins Hosp. 72: 65, 1943.
20. Duff, G. L.: Quoted in Simon, M. A.: Pathologic Lesions Following the Administration of Sulfonamide Drugs, Am. J. M. Sc. 205: 439, 1943.
21. Longscope, W. T.: Serum Sickness and Analogous Reactions From Certain Drugs Particularly the Sulfonamides, Medicine 22: 351, 1943.
22. Black-Schaffer, B.: Pathology of Anaphylaxis Due to Sulfonamide Drugs, Arch. Path. 39: 301, 1945.

Clinical Reports

COR BILOCULARE

CASE REPORT

J. K. BEMBENISTA, M.D.

BUFFALO, N. Y.

COR BILOCULARE is a rare congenital cardiac anomaly and was first recorded by Wilson in 1798. Abbott, in a comprehensive study of congenital heart lesions published in 1936, recorded only fourteen examples of this anomaly. Since then, five additional cases have been reported, two of which occurred in twins.

Most subjects with this condition die in early infancy, although one patient lived to the age of 18 years. The sex distribution is about equal. There are no characteristic physical signs; no cardiac murmurs or thrills have been described. Cyanosis is the most prominent finding. Other anomalies may be associated with this condition, the commonest of which is a persistent truncus arteriosus.

CASE REPORT

On March 12, 1941, a white baby girl, weighing 8 pounds and 11 ounces, was born at the Mercy Hospital. The delivery was spontaneous from a vertex presentation under vinethene anesthesia.

The mother was 36 years of age and has five other normal children. Her past history is not remarkable. The child's father is living and well.

Immediately after delivery the child's color was good and it had a strong cry. About three hours later, it was observed that the baby became cyanotic when she cried. Examination of the infant at this time revealed no other abnormalities. No murmurs were heard over the precordium. An x-ray film showed no enlargement of the thymus gland.

For the first few days of life the baby's color was fair until it sneezed or cried; then cyanosis became pronounced. Later cyanosis became constant and was not relieved even when oxygen was given continuously. The baby had several vomiting spells with emesis of blood-streaked mucus. Its condition became progressively worse, and it expired the seventh day after birth.

Autopsy Findings.—External examination showed a well-developed and fairly well-nourished but cyanotic female infant; the only abnormality was a small angioma of the skin of the back. Examination of the internal organs revealed no important findings except in the heart.

When viewed in situ, the portion of the heart usually formed by the right auricle was seen to be slightly enlarged; the part of the left border of the heart usually formed by the left ventricle appeared more globular than usual. The pulmonary artery was in its proper position. The ductus arteriosus was present but somewhat narrow, especially in its mid-portion.

On opening the heart only one atrial chamber was found, from which two auricular appendages projected and into which all the veins entered. The common atrium communicated through a large aperture with a thick-walled ventricle, which in turn emptied into a normal-sized aorta. Near the upper margin of the ventricle and in its anterior wall lay a small, flat, slitlike cavity which evidently was a rudimentary right ventricle. It communicated with the pulmonary artery by an opening guarded by three small but normal valve cusps. Although this chamber communicated with the large ventricle by a tiny orifice, it contained no blood and apparently did not function. This infant's heart thus had only one atrium, one useful ventricle, one rudimentary and nonfunctioning ventricle, and a small ductus arteriosus. Blood entered the pulmonary artery only through this insufficient ductus arteriosus.

On more detailed examination it was found that four large veins entered the atrium. On the right side superiorly was the opening of the superior vena cava. The posterior margin of this opening was formed by a small muscular bundle, forming a semilunar ridge. This normally is the upper limbus of the foramen ovale. Posterior to and just below the orifice of the superior vena cava, the right and left pulmonary veins entered. Below these lay the opening of the inferior vena cava. This opening was partly covered by a fibromuscular membrane which most likely was the rudiment of the interatrial septum. The opening of the coronary sulcus lay between that of the inferior vena cava and the atrioventricular aperture.

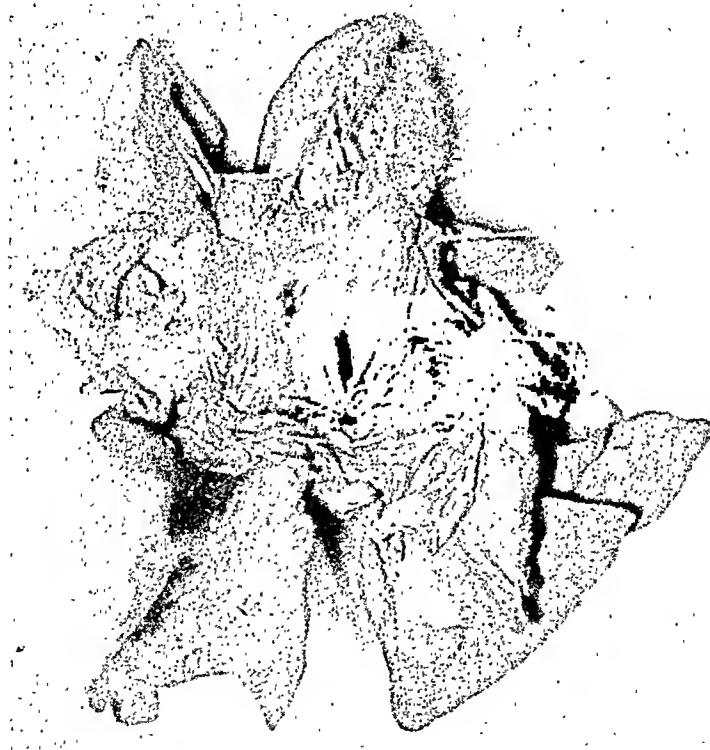


Fig. 1.—The single auricle and the only functioning ventricle are shown.

The atrioventricular opening was 4 cm. in circumference and was guarded by four unequal valve leaflets, to which were attached four groups of papillary muscles.

The ventricle was as large as the combined right and left ventricles of a normal heart at birth. The thickness of its muscle wall averaged 6 millimeters. From its superior portion arose the aorta with a normal semilunar valve composed of three cusps. Just below the base of the right posterior cusp of this valve was a tiny opening in the wall of the ventricle. This tiny orifice was the only communication between the large ventricle and the slitlike cavity of the rudimentary right ventricle previously described.

The pulmonary artery was in its normal position and was guarded by three small cusps of the pulmonary valve. The coronary arteries were not remarkable.

The lungs, liver, spleen, and kidneys showed passive congestion.

SUMMARY

The heart described was unusual in that it consisted primarily of only one atrium and one ventricle with a patent ductus arteriosus. The ventricle had a rudimentary slitlike cavity in its wall, but this to all intents and purposes was nonfunctioning.

This case, we feel, is a cor biloculare.

REFERENCES

1. Tow, A.: Cor Biloculare With Truncus Arteriosus and Endocarditis, *Am. J. Dis. Child.* 42: 1413, 1931.
2. Abbott, M. E.: *Atlas of Congenital Cardiac Disease*, New York, 1936, The American Heart Association.
3. Davies, F., and MacConaill, M. A.: Cor Biloculare With Note on Development of Pulmonary Veins, *J. Anat.* 71: 437, 1937.
4. Guistra, F. X., and Tosti, V. G.: True Cor Biloculare in Identical Twins, *AM. HEART J.* 17: 249, 1939.
5. Benjamin, J. E., Landt, H., and Zeek, P.: Persistent Ostium Arterioventriculare Commune in Heart Which Functioned as Biloculate Organ; Report of Case, Including Autopsy, in an Eighteen-Year-Old Girl, *AM. HEART J.* 19: 606, 1940.
6. Rossman, J. I.: Cor Biloculare With Transposition of Great Cardiac Vessels and Atresia of Pulmonary Artery, *Am. J. Clin. Path.* 12: 534, 1942.
7. Michelson, R. P.: Cor Biloculare With Persistent Truncus Arteriosus, *AM. HEART J.* 25: 112, 1943.

Letters

TO THE EDITOR:

In a paper in the April, 1946, issue of the AMERICAN HEART JOURNAL (vol. 31, pp. 473 to 476) on the duration of the P-R interval and its relationship to the cycle length, the author states: "It is seen that although there appears to be a tendency for the P-R interval after exercise to be shorter, the difference is more apparent than real. For the P-R values after exercise to be significantly different from those found before exercise, a difference greater than three times the standard deviation should be present. In this series the difference was less than even twice the standard deviation." Table II (p. 476) shows in a large number of young men a mean P-R interval of 0.143 sec. and a standard deviation of 0.014 sec. before exercise, and of 0.129 and of 0.010 sec., respectively, after exercise. It is not clear whether the author refers in the section quoted to *mean* P-R values or to the P-R interval in the individual case. His own data (Fig. 1, p. 474) show definitely that the mean P-R interval is shorter at short than at long cycle lengths. This is demonstrated by the following facts: The mean P-R interval of the 189 individuals (Fig. 1) whose cycle lengths were below 0.46 sec. is 0.123 ± 0.00068 sec., and the standard deviation is 0.014 ± 0.00047 sec. The 160 individuals whose cycle lengths exceed 0.79 sec. have a mean P-R interval of 0.1475 ± 0.00091 sec. and a standard deviation of 0.017 ± 0.00064 sec. The difference between the means is 0.0247 ± 0.00114 sec., or over twenty times its probable error. (See Raymond Pearl, *Introduction to Medical Biometry and Statistics*, Philadelphia, 1930, W. B. Saunders Co., p. 283, et. seq.) Hence it is clear that the *mean* P-R interval shortens as the heart rate increases, and there is no doubt, in view of the large number of persons studied, that the figures given by the author in his Table II prove this just as conclusively as the above analysis. In contrast to these statements about the mean interval, in the *single* case among healthy male adults in the age range studied, the P-R being measured by the author's technique, the odds against the interval falling outside the range set by three standard deviations is about 370 to one.

In an earlier paper (AM. HEART J. 31: 329, 1946) the same author states that the relationship between the Q-T interval and the cycle length is linear. In this case it is also possible to demonstrate from the data given on p. 330 that the relationship in question is actually curvilinear (Pearl: p. 386 et seq.), and this evidence becomes overwhelming when the data supplied by other authors are also treated statistically.

RICHARD ASHMAN

LOUISIANA STATE SCHOOL OF MEDICINE, NEW ORLEANS.

The following is a reply to Dr. Ashman's letter:

TO THE EDITOR:

In the section of the paper quoted (vol. 31, p. 473) and Table II (p. 476), the mean P-R values referred to are the means of all the individual P-R measurements. This was broken down into (a) the mean value of all the P-R intervals before exercise, and (b) the mean value of all the P-R intervals after exercise. Thus, a comparison was made between the P-R intervals of the same individual or group at different heart rates. However, no such comparison between individuals was made or implied by this treatment of the data. This treatment was used to indicate what the chances were for a healthy male individual chosen according to the criteria outlined in the article to show differences between P-R intervals at different heart rates greater than three standard deviations. As Dr. Ashman points out, the odds are approximately 370 to one against such an occurrence.

The second point made by Dr. Ashman, that the mean P-R interval shortens as the cycle length shortens, does not contradict any statement in the article. Not only does Fig. 1 (p. 474) show this to be true, but the coefficient of correlation that was calculated and found to be plus 0.387 shows this even more clearly. Yet, what does this mean? Showing that the P-R interval is shorter at shorter cycle lengths is only a qualitative analysis. When this is studied quantitatively by determining the coefficient of correlation it is found that, although there was such a relationship between P-R and C, the low order of magnitude of this coefficient indicates that this relationship is not of importance.

In studying the relationship of QT to cycle length (vol. 31, p. 329), Fisher's method of analysis of variance was used to determine whether or not the actual data deviated significantly from linearity. It was found that the deviation was not significant. This method was used because it was recognized as one that would give an accurate analysis of the data. Dr. Ashman applied another method of analysis to the same data. I agree with Dr. Ashman that, when this other method, the Correlation Ratio (η^2) and Blakeman's Criterion, is used, there appears to be significant deviation from linearity. The question that arises is why should the same data, when analyzed by two methods, yield different interpretations. Apparently, the difference arises from the methods used. The Correlation Ratio and Blakeman's Criterion do not take into account the number of assays. A more detailed discussion of this can be found in Fisher, R. A.: *Statistical Methods for Research Workers*, ed. 6, p. 263. Because of the limitations inherent in the latter method, Fisher's method of analysis of variance was felt to be the more desirable and more accurate.

There is one point I wish to make. In analyzing the data it was realized that our data formed a regression within certain limits. Thus, we were studying only one segment of a curve or line that theoretically may extend much beyond the limits set by our study. Let us assume for argument's sake that this segment is part of a curve or even a circle. This circle may have a radius of such magnitude that the regression set by our limits forms a relatively small segment of this circle. It is known that as the ratio of segment to radius becomes smaller and approaches zero, the segment approaches a straight line. Thus, the QT/C regression studied here may be a small segment of a much greater curve, and analysis of this segment per se may fail to reveal significant deviation from linearity when only 1,400 measurements are used. However, if 14 million measurements were analyzed we might then find that the deviation from linearity which was not significant when 1,400 were studied is now significant.

Thus, although this study failed to reveal significant deviation from linearity, it is understood that the regression might still be curvilinear. For practical purposes, however, treating this data as a linear regression is adequate.

ISIDORE SCHLAMOWITZ, M.D.

Abstracts and Reviews

Selected Abstracts

Henry, G. C., and Boone, A. A.: Electrocardiograph for Recording Heart Motion Utilizing the Roentgenoscope. Am. J. Roentgenol. 54: 217 (Sept.), 1945.

Although graphic recording of the motion of the heart and great vessels has been a long-desired goal, this method has not been used extensively because of analytic difficulties in the size, clarity, and brevity of the recorded waves to be examined on the kymogram and the time-consuming nature of the analysis. The authors have developed a method which overcomes these difficulties and produces a large, beam type or electrocardiographic type of tracing on bromide paper of a chosen point of the cardiac silhouette.

Under the roentgenoscope, the diaphragm of the electrocardiograph, which contains a narrow slit, is aligned at right angles to the particular portion of the heart border to be investigated. As the heart beats, its border moves back and forth across the slit, varying the intensity of the roentgen rays passing through it. If the intensity of these rays were recorded with distortion in respect to a time axis we would have an indication of the motion of this portion of the heart border. This is accomplished by a 931-A multiplier phototube, used by Morgan in his exposure meter for roentgenography. A strip of fluorescent screen is placed directly over the photosensitive area of the 931-A tube. As roentgen rays strike the tube, the cathode is illuminated. When the shadow of the heart border moves inward (contractile motion) this strip of screen is further irradiated by the beam. Thus, the total light emitted is proportional to the changes in the position of the heart border. The current output is amplified and recorded by a galvanometer. Tracings of the carotid pulse are recorded simultaneously to align curves from separate points on the cardiac border in respect to the time relations in the cardiac cycle.

Sample records are presented which represent the motion of the left ventricular border, the pulmonary artery, the aortic knob, and the right auricular border. These are aligned, one above the other, by the carotid pulse tracing, so that events or different records falling on any given vertical line occur at the same time. The wave forms for each of the border areas of the heart are found to be characteristic of that particular area and they resemble closely the respective volumetric wave forms found in physiology texts.

These authors expect to present more detailed information regarding the individual chambers of the heart in subsequent papers. SERBER.

Dobson, C.: Subacute Bacterial Endocarditis Complicated by Pregnancy, Successfully Treated With Penicillin. Am. J. Obst. & Gynec. 51: 427 (March), 1946.

The patient, a 24-year-old gravida ii, para 0, entered the hospital Jan. 2, 1945, for a therapeutic abortion. She gave a history of having had a cold for the preceding two weeks, complicated by backache, low-grade fever, nausea, and occasional tenderness in several of the digits. She presented evidence of rheumatic mitral and aortic disease, and two blood cultures were positive for *Streptococcus viridans*. Penicillin administration was begun on Jan. 14, 1945; 200,000 Oxford units were given daily in divided doses. On January 13, the blood culture was negative. Repeated subsequent cultures were negative. After five weeks of penicillin therapy her progress was not satisfactory, and it was considered advisable to interrupt the pregnancy, which was

terminated on the nineteenth of February. The patient was discharged on March 18, 1945, nine days after penicillin was discontinued. The cardiac reserve was good, and the patient was considered to have recovered from subacute bacterial endocarditis. BELLET.

Hunter, W. S.: Coronary Occlusion in Negroes. J. A. M. A. 131: 12 (May 4), 1946.

This author, after reviewing the literature and as a result of his own observations and experiences, concludes that the diagnosis of coronary occlusion is rarely made ante mortem in Negroes. He gives as reason for this the fact that, during the episode of coronary occlusion, dyspnea is the chief complaint and pain is absent. He reviewed a series of 1,000 consecutive autopsies on Negroes and 1,000 consecutive autopsies on white patients at the Louisville General Hospital over a ten-year period. He found that below the age of 70 years the incidence of myocardial infarction was approximately the same in both Negro and white patients. Dyspnea rather than substernal pain was the outstanding presenting symptom in all the Negroes prior to death.

Hunter stresses the point that careful clinical and electrocardiographic examination of Negroes with acute left ventricular failure will reveal many diagnoses of coronary occlusion. BELLET.

Weinroth, L. A., and Herzstein, J.: Relation of Tobacco Smoking to Arteriosclerosis Obliterans in Diabetes Mellitus. J. A. M. A. 131: 205 (May 18), 1946.

The purpose of this study was to determine the relative incidence of occlusive arterial disease in diabetic patients who smoked, as compared with a similar group who abstained from the use of tobacco. The findings indicate the significantly higher incidence of occlusive vascular disease in diabetic patients who used tobacco as compared with diabetic nonsmokers. This held true in all decades up to 70 years. The reason for the increased frequency of occlusive arterial disease which they have observed in diabetic smokers is not clear. The authors suggest that over a period of time by virtue of its vasoconstrictor effect, tobacco may cause an already constricted arteriosclerotic vessel to become still further narrowed. Such encroachment on the lumen would favor thrombus formation. A lowered frequency of arteriosclerosis obliterans prevailed in general among nonsmokers regardless of such factors as severity of the illness, adequacy of control, and the presence of obesity or hypertension. BELLET.

Bauer, G.: Heparin Therapy in Acute Venous Thrombosis. J. A. M. A. 131: 196 (May 18), 1946.

This author differentiates between the inception and course of occlusive disease of the superficial and deep veins. In superficial veins, thrombophlebitis is the primary disorder and is followed secondarily by thrombotic obliteration of the venous segment involved. In the large deep veins of the legs the process begins with a thrombus which arises in a muscle vein and projects into the lumen of one of the large venous trunks of the lower part of the leg. Here it becomes the starting point for the deposition of a thrombus which extends upward and, in about 80 per cent of the cases, reaches the femoral vein. This process, which generally lasts about twenty-four to forty-eight hours, may result either in the formation of an embolus, or, by far the most common course, the thrombus may grow in thickness and block the lumen of the femoral vein along its entire length and produce typical phlegmasia alba dolens. Complications of this process in the chronic stage are permanent swelling of the legs, indurative lesions, and leg ulcers in a large percentage of cases. The author emphasizes the importance of early diagnosis of this condition which is suggested by the presence of tenderness in the back of the calf accompanied by mild swelling and pain in this region. The diagnosis is confirmed by phlebography which presents a rather characteristic picture. The opinion is given that phlebography should constitute a routine method of study in all cases of suspected early thrombosis. Remarkable improvement followed the early institution of heparin therapy. In addition, forceful active leg movements were instituted immediately after the diagnosis was established. The mortality from thromboembolism under this

treatment was decreased to less than one-tenth of what it formerly had been. The length of stay in bed was reduced from forty days to less than five days, and incapacitating aftereffects did not appear in the majority of cases so treated.

BELLET.

Manchester, R. C.: Rheumatic Fever in Naval Enlisted Personnel. III. The Physiologic and Toxic Effects of Intensive Salicylate Therapy in Acute Cases. J. A. M. A. 131: 200 (May 18), 1946.

Following the regimen outlined by Coburn, thirty-five patients with acute rheumatic fever received daily intravenous doses of 10 Gm. of sodium salicylate dissolved in 1 liter of saline solution or Ringer's lactate solution for four to ten days. Nineteen additional patients received oral therapy throughout the course of treatment, which consisted of between 10 and 12 Gm. of acetylsalicylic acid or sodium salicylate daily, usually in conjunction with 8 Gm. of sodium bicarbonate. Under this regimen, toxic reactions of serious proportions occurred, but these were preventable in most instances. Hypoprothrombinemia occurred frequently, reaching a maximum in the first week of salicylate administration, but improved spontaneously thereafter even though large doses were continued. No instance of hemorrhage as a result of hypoprothrombinemia was observed. The alkali reserve was depleted unless adequate amounts of alkali were given in conjunction with salicylates. When large doses of salicylates were given orally, between 0.8 and 1 Gm. of sodium bicarbonate was given with each gram of salicylate. For the same reason, intravenous salicylates should be administered in Ringer's lactate solution instead of saline solution.

Severe delirium, "acute salicylism," is dependent on the rapid rise in blood salicylate levels associated with intravenous therapy and occurs most often in acutely ill patients who have not built up an antecedent tolerance to the drug. It was not observed in this series, following oral therapy.

The author found that serum salicylate levels of 25 mg. per 100 c.c. or higher have been found to suppress rheumatic infection satisfactorily. Salicylate therapy was continued until the erythrocyte sedimentation rate had been normal for two weeks.

BELLET.

Bourne, G.: Bicuspid Aortic Valve Diagnosed During Life. Brit. M. J. 1: 609 (April 20), 1946.

This author discusses criteria upon which he believes a diagnosis of bicuspid aortic valve may be made during life. These are the appearance of the signs and symptoms of subacute bacterial endocarditis and accompanying aortic insufficiency in an individual, usually young, who has previously been carefully examined and in whom there was no evidence of heart disease of any kind. Since bacterial endocarditis rarely develops upon a normal aortic valve, the sudden appearance of aortic regurgitation together with infective symptoms in a previously normal person is extremely suggestive of the presence of a bicuspid valve. The diagnosis was made in life and confirmed by necropsy in a case presented by the author.

BELLET.

Lenegre, J., and Maurice, P.: Some Results of Recording Electrical Currents From the Right Auricle and Ventricle by the Direct Intracavity Lead. Arch. d. mal. du coeur. 38:298 (Nov.-Dec.), 1945.

The authors report some of their results in electrocardiograms recorded from within the right auricle and ventricle in man. Their technique involved the use of a soft exploring electrode of tin which projects from the end of a No. 13 ureteral catheter. A gold wire in the lumen of the catheter connected the lead wire to the electrode. The catheter was inserted into an antecubital vein and, under fluoroscopic observation, was passed into the right auricle or ventricle. The indifferent electrode was placed on the left leg. The intra-auricular and intraventricular leads were recorded simultaneously with the three limb leads.

Records obtained from within the right auricle showed rapid auricular waves of considerable amplitude which were often analogous to those obtained from an esophageal lead. Records ob-

tained from within the right ventricle indicated clearly the sequence of ventricular activation in extrasystoles and in bundle branch block. Current views on the interpretation of electrocardiograms in these conditions were confirmed.

It is emphasized that electrocardiograms from the intracavity leads must be interpreted with some caution because of artefacts which are inherent in the technique. There is no certainty as to which part of the cavity wall is in contact with the electrode nor is there any assurance that the contact is constant because of the movements of the heart. Some of the resultant artefacts are obvious, but others may be less apparent. The procedure is considered valuable, however, for the study of arrhythmias and conduction defects.

LAPLACE.

Pruche, A: Cardiodynamometry. A Practical Test for Determination of the Functional Capacity of the Heart. Arch. d. mal. du coeur. 38:264 (Nov.-Dec.), 1945.

The author states that the criterion for the functional capacity of the left heart is the supply of an adequate amount of blood to the peripheral tissues in proportion to their activity, while that of the right heart is the withdrawal of an adequate amount of blood from the venous system to prevent peripheral congestion. As a test of cardiac function based on this concept, he uses the following procedure. The patient is placed in a recumbent posture with one arm held at a right angle to the body. An armlet connected to a water manometer is placed on the upper arm. A second armlet connected to a plethysmograph is placed on the lower arm. The subject rises, performs a standard exercise of twenty deep flexions of the legs, and lies down. Measurements of the circulation are made immediately. The subject then rises, makes fifty deep flexions, and again lies down, whereupon the measurements are repeated.

Three determinations are made. The first concerns the pressure in the return circulation (PV). The pressure in the upper armlet is gradually increased and a notation is made of the level at which beginning congestion in the lower arm is indicated by the plethysmograph. This is considered to be the venous pressure in the arm. The second determination concerns the systolic index (IS). At the moment of recording PV, the upper armlet pressure is rapidly increased to 80 cm. of water and the resulting upward deflection of the plethysmographic indicator for a period of exactly ten seconds is recorded. The third determination concerns the volumetric index (V). This is the relation of IS to the number of pulses noted during ten seconds from the moment of establishing the IS. It represents the volume of blood entering the distal segment of the limb.

Criteria for a normal cardiodynamic status are: For PV, constant or little variation throughout the test; for IS, in relation to its control valve, IS increases two points for the first exercise and four points for the second; for V, no significant change.

Results of the application of this test to ambulatory cardiac patients are reported. It is emphasized that a normal test does not necessarily indicate absence of organic heart disease, nor does an abnormal result indicate the existence of organic heart disease. The test affords simply a quantitative estimate of the functional capacity of the heart.

LAPLACE.

Penner, S. L., and Peters, M.: Longevity With Ventricular Aneurysm; Report of a Case With a Survival Period of Fifteen Years. New England J. Med. 234:523 (April 18), 1946.

The case is reported of a 43-year-old infantry officer who had a severe anginal attack in October, 1929. A second attack, accompanied by shock and an audible friction rub occurred in November, 1929. A third attack, also accompanied by an audible friction rub, occurred in January, 1930. The electrocardiogram showed evidence of a typical acute anterior infarction. Recovery ensued without congestive failure but the patient remained in the hospital for one year. Thereafter he led an active life and in September, 1942, he returned to the Army on limited duty. In September, 1944, he had a recurrence of moderate anginal pain and dyspnea on effort. X-ray examination showed slight cardiac enlargement and, overlying the left ventricular portion of the cardiac silhouette, a thin curvilinear band of calcification forming the outer half of a soft tissue condensation. Fluoroscopy revealed that the calcification was in the outer surface of an outpouching

of the anterior surface of the left ventricle. No pulsation in the area was noted. A diagnosis of left ventricular aneurysm with calcification of the ventricular wall was made. The patient's symptoms subsided and when last seen on Sept. 6, 1945, he was feeling well and enjoying deep-sea fishing.

It is pointed out that the aneurysm in this case had probably been present for fifteen years. The fact that the patient remained in the hospital for an entire year following his initial illness is considered responsible for the unusual degree of recovery.

LAPLACE.

Stearns, S., Riseman, J. E. F., and Gray, W.: Alcohol in the Treatment of Angina Pectoris. *New England J. Med.* 234:578 (May 2), 1946.

Observations were made on the therapeutic effect of alcohol in a series of twenty-one patients who had angina of effort. The series included nineteen men and two women. Their ages ranged from 39 to 75 years. Only one had had recent cardiac infarction and none had congestive failure. Control determinations were made of the patients' ability to work by subjecting them to the Standardized Exercise Tolerance Test which consists of continuously ascending and descending a two-step staircase in a cold room. The effect of alcohol was then studied by repetition of the test.

Twenty-one patients took one ounce of whisky at various times up to ninety minutes before the test. Five of the patients were able to perform from 18 to 27 per cent more work than was otherwise possible. Nine patients drank one ounce of whisky four times daily for a week prior to the test. Of these, two patients had no attacks of pain during the week but had no demonstrable increase in exercise tolerance, while in two patients, the angina became worse during the week. Five patients felt subjectively better; in one, exercise tolerance was increased 23 per cent and in another, it was decreased 33 per cent.

When one-half ounce of whisky was held in the mouth during the test in order to demonstrate a possible reflex effect, there was no change in pain or in exercise tolerance.

It is concluded that therapeutic doses of whisky do not measurably shorten the duration of attacks or increase the work capacity of patients who have angina pectoris. Many patients are afforded an increased sense of well-being but others are made worse.

LAPLACE.

Froment, R., Guinet, P., Vignon, G., and Martin-Noel: Atheromatous Coronary Disease of Early Onset and Parallel Course in Twins. *Arch. d. mal. du coeur.* 38:260 (Nov.-Dec.), 1945.

Two cases are reported of homologous twins who were apparently in excellent health until the age of 34 years when, within a few weeks of each other, both began to have typical severe angina of effort. Both had mild hypertension. Nine months later, the first twin died suddenly after several days of recurrent spontaneous anginal attacks. Autopsy showed almost complete atheromatous obliteration of all the large coronary arteries together with diffuse myocardial degenerative change.

In the case of the second twin, the angina of effort persisted for several months but by the following year had disappeared completely. Three years later, angina reappeared in mild form and then suddenly a severe spontaneous attack occurred, during which the patient died. No autopsy was performed but an electrocardiogram taken two years previously had shown flat T_z and a deeply negative pointed T_z .

These cases emphasize strongly the familial character of coronary artery disease.

LAPLACE.

Froment, R., and Gonin, A.: Aortic Stenosis Due to Calcified Syphilitic Valvulitis. *Arch. d. mal. du coeur.* 38:257 (Nov.-Dec.), 1945.

Three cases are reported in which aortic insufficiency caused by syphilitic valvulitis was accompanied by a substantial degree of stenosis. Autopsy revealed that the cause of the stenosis

in all cases was secondary calcification which had involved a sufficient area of the affected valves to prevent their complete opening.

It is pointed out that aortic stenosis of sufficient degree to be recognized clinically is generally considered to be evidence against syphilis as the cause of the valve lesion. The three reported cases are cited as exceptions to this rule. It remains true that syphilis does not produce aortic stenosis but there are, nevertheless, rare instances of syphilitic aortic valvulitis in which a moderate degree of stenosis may occur as a result of partial secondary calcification of the valve leaflets.

LAPLACE.

Lium, R.: Cardiac Arrest After Spinal Anesthesia. Report of a Case With Recovery. New England J. Med. 234:691 (May 23), 1946.

The case is reported of a 62-year-old woman who was admitted to the hospital for a cholecystectomy. No preoperative cardiovascular abnormality was noted except a blood pressure of 180/90. The preoperative medication included pentobarbital sodium, 0.2 Gm., at bedtime, which was repeated one hour before operation, and morphine sulphate, 10 mg., one-half hour before operation. Spinal anesthesia was effected by pontocaine, 18 mg. in 3 c.c. of 10 per cent glucose, placed in the subarachnoid space through the third lumbar interspace. Operation was begun eleven minutes after the administration of the anesthetic. The patient stopped breathing forty-three minutes later. A right rectus incision had been made and the heart could be palpated through the diaphragm. No impulse was detectable. Cardiac massage was immediately instituted by compressing the heart against the chest wall. With each compression the heart flickered a little more firmly and a slow spontaneous beat was suddenly established five minutes from the onset of cardiac arrest. Blood pressure immediately rose from 0 to 170/90. Periods of artificial respiration had been alternated with those of cardiac massage. Spontaneous respiration was resumed thirty-five minutes later and the operation was completed.

The patient's general response for twenty-four hours after operation was that of a decerebrate, but complete recovery occurred during the next three days. The precise mechanism of this type of anesthetic accident is undetermined. In most cases, cardiac massage and artificial respiration with pure oxygen are capable of reviving the heart.

LAPLACE.

Bridges, W. C., Wheeler, E. O., and White, P. D.: Low-Sodium Diet and Free Fluid Intake in the Treatment of Congestive Heart Failure. New England J. Med. 234:573 (May 2), 1946.

The treatment of cardiac edema by restricting sodium and permitting a free fluid intake has not yet received wide application, although its usefulness is now generally appreciated. At the Massachusetts General Hospital, sixty-four patients who had congestive heart failure were treated by this technique as well as with digitalis, diuretics, and other routine measures. Seventeen patients obtained much help, fifteen moderate benefit, eight slight benefit, and seven no benefit. In the remaining seventeen cases, the patients were either uncooperative or the data were insufficient to warrant inclusion in the present report.

The diet used contained about 700 mg. of sodium in an amount of food equivalent to 1,800 calories. If the food tasted too flat, ammonium chloride was used in place of salt. It was essential that no salt or soda be used in cooking or included in incidental medicines.

The advantages of the treatment are that it frequently permits control of edema that cannot be controlled otherwise, diminishes the frequency with which mercurial diuretics must be given, and enables the patients to take more water. The disadvantages are the difficulty of preparing or obtaining the diet outside of a hospital and the flat taste of the food.

The optimum amount of water to be taken has not yet been determined and it is uncertain whether 5,000 to 6,000 c.c. per day is more beneficial than 2,000 to 3,000 c.c. Undoubtedly, however, the water intake formerly recommended was distinctly inadequate because diminished renal function often prevents sufficient excretion of waste products when the daily fluid intake is less than 1,500 c.c.

LAPLACE.

Bachman, A. L.: Quantitative Roentgenographic Method for the Determination of Left Auricular Size. *Am. J. Roentgenol.* 55:427 (April), 1946.

The importance of roentgenographic evidence of enlargement of the left auricle in the diagnosis and management of rheumatic heart disease is at present generally accepted. The roentgenographic recognition of normal or markedly enlarged left auricles offers little difficulty. However, considerable difficulty is encountered in the diagnosis of slight enlargement of the left auricle. Much of this difficulty is due to the wide variation in the outline of the auricle in normal cases and to the absence of a sharply defined difference between the appearance of the normal and minimally enlarged auricular chamber.

The purpose of this paper is to demonstrate the amount of roentgenographic variation in the appearance of the left auricle in healthy individuals and to furnish quantitative standards establishing the distribution range for this normal variation. The anatomy of the esophagus and its relation to the neighboring structures in the anteroposterior and the oblique views is discussed in detail. At the site of the three main impressions, the aortic, the pulmonary, and the left auricular, the esophagus shows local posterior bulges but resumes its general downward and anterior direction immediately below the indentations. A short distance (0.7 cm.) below the lower end of the aortic indentation is the inconstant bronchial impression. The best indicator of the general esophageal course is the direction of the "alpha" segment, which is located below the bronchial indentation, since there are no local impressions by adjacent viscera on this portion of the esophagus. The angle which the posterior border of the opacified esophageal "alpha" segment makes with the vertical axis has been designated as "gamma" and is an index of the general esophageal course. The angle between the downward extension of the posterior border of the "alpha" segment, and the posterior margin of the esophagus in the upper portion of the auricular impression has been designated as the angle "theta."

The left auricle, as it enlarges, expands in a posterior direction early in its course; upward enlargement is usually seen shortly afterward. Posterior displacement is indicated in the early phases by an increase in the angle between the lower end of the "alpha" segment and the upper portion of the auricular impression (that is, the angle "theta").

Methods were therefore employed to yield quantitative measurements for the indices of left auricular size: (1) the angle "theta," (2) "M. P.," which is the distance from the most posterior point on the posterior border of the esophagus in the auricular region to a vertical line dropped from the most posterior point on the border of the esophagus to the region of the aortic knob indentation, and (3) the angle "gamma." A series of other measurements, namely, (a) the height and weight relationship, (b) frontal cardiac area, (c) transcardiac diameter, and (d) thoracic height, were also made and statistical correlations calculated between these external somatic factors and the three main indices.

Two hundred fifty healthy male soldiers between 18 and 30 years of age were selected following a physical examination in which rheumatic and other types of heart disease were ruled out. A set of four roentgenograms were obtained for each examinee, measurements as outlined were made, and a series of normal standards created. The views employed were posteroanterior in mid-inspiration, right anterior oblique in mid-inspiration, left lateral in mid-inspiration, and right anterior oblique in mid-expiration.

The quantitative analysis method was found not only of great aid in establishing the diagnosis of slight left auricular enlargement, but also was of considerable value in following patients where the diagnosis was made in the initial examination. In the presence of conditions which grossly alter the course of the esophagus, measurements were obviously invalid. These conditions included aneurysm of the aorta, substernal goiter, arteriosclerosis with tortuosity, mediastinal tumors, pulmonary fibrosis, and pericardial effusion.

BELLET.

Gravelle, L. J., and O'Donnell, C. H.: Lumbar Sympathectomy for Chronic Leg Ulcers. *Am. J. Surg.* 71:620 (May), 1946.

Twenty-one patients with chronic leg ulcers were treated by lumbar sympathectomy with good results in twenty. The ulcers were due to venous stasis, arterial disease, and trauma.

A rise in skin temperature after lumbar paravertebral block was used as a criterion in selecting patients for sympathectomy. Removal of the second and third lumbar ganglia proved satisfactory for sympathetic denervation of the lower extremity. NAIDE.

Farinas, P. L.: Retrograde Abdominal Aortography. *Am. J. Roentgenol.* 55:448 (April), 1946.

The author describes his technic of retrograde abdominal aortography. The patient is sedated with a barbiturate the night before and morphine is administered one hour before the procedure. Prior to injection, the femoral artery is exposed by blunt dissection under local anesthesia at the level of the triangle of Scarpa and is punctured with a trochar 1.5 mm. in diameter, through which injection of 50 c.c. of a 70 per cent solution of Diodrast is made in two and one-half to three seconds. Tourniquets must be placed at the roots of both lower extremities in order to produce a slowing of the circulation. The Trendelenburg position may be required in certain cases. To avoid changes in pressure due to inertia and cardiac systole, the author uses a specially designed pump with a piston which acts upon the embolus of the syringe. The piston works by an air compressor with a regulator and a manometer. By this means 25 c.c. of the opaque solution per second can be injected through the trochar, with a constant pressure of 15 pounds. The first roentgenogram is taken when 40 c.c. of the opaque substance has been injected and the second one immediately after completion of injection, using a fast plate changer. The trochar is withdrawn when the injection is finished, and the adventitia of the artery and wound is closed.

By this method pathologic changes in the aorta and its branches can be clearly visualized and studied. Roentgenograms are presented in cases of atheromatous degeneration of the aorta and iliac arteries, aneurysm of the abdominal aorta, uterine fibroma, ovarian cyst, and visualization of the renal circulation. By means of urograms taken at the same time, valuable information concerning renal function is obtained, and thus a method of further study of renal pathology is presented. The author hopes that retrograde abdominal aortography will become a common method of clinical investigation and diagnosis. SERBER.

Cook, W. T., Cloake, P. C. P., Govan, A. D. T., and Collbeck, J. C.: Temporal Arteritis: A Generalized Vascular Disease. *Quart. J. Med.* 15:45 (Jan.), 1946.

The thesis is presented that there exists in elderly people a widespread arterial disease, not uncommon but rarely recognized, in which characteristic arterial and striking local signs occur. The inflammatory and degenerative changes in the walls of the affected arteries produce a characteristic histologic picture. The case histories of seven such patients with temporal arteritis are presented. The symptoms and signs in this group, together with those from the thirty-one cases reported in the literature, are described.

The characteristic clinical features are anorexia, loss of weight, joint and muscle pains, pyrexia, painful arterial thrombosis, and severe headaches, occurring in elderly patients. At least one-half the patients so far reported have had visual disturbances leading in many instances to complete loss of sight. Post-mortem examination was carried out in two cases. A characteristic histological picture was noted in the aorta and in the temporal, radial, subclavian, femoral, coronary, renal, retinal, coeliac, and mesenteric arteries. Involvement of the femoral vein was found in one case.

The pathological features are those of a subacute inflammation spreading probably by the vasa vasorum to the media. The internal elastic lamina appears to cause the inflammation to spread longitudinally. The lamina may be destroyed and in the process of healing, new reduplicated layers are formed. The intima becomes hypertrophied and thrombosis is a common sequel. Pathologically the vascular disease differs from thromboangiitis obliterans and periarteritis nodosa.

The prognosis is relatively good as regards life, though it may be fatal in some cases. Though the generalized character of the disease is emphasized, the term temporal arteritis has been retained as indicating a specific clinical entity in the absence of any definite etiological factor. NAIDE.

Faust, F. L.: Repeated Sympathetic Blocks: Their Limitation and Value. *Anesthesiology* 7:161 (March), 1946.

The value and limitation of repeated sympathetic blocks are emphasized. This form of therapy is useful in diseases of the arterial and venous systems, particularly in acute and chronic thrombophlebitis, post-traumatic dystrophies, traumatic shock associated with a crushing wound of an extremity, various inflammatory processes, herpes zoster, and joint stiffness. The technics of lumbar and cervical blocks are described. NAIDE.

Weeks, D. M., Steiner, A., and Victor, J.: Splenorenopexy in Essential Hypertension. *Surgery* 19:515 (April), 1946.

Splenorenopexy in the dog with bilateral constriction of the renal arteries produces a collateral circulation from the spleen to the capillaries about the convoluted tubules of the renal cortex. A reduction in blood pressure occurs in hypertensive dogs following splenorenopexy. It was therefore decided to test the effects of splenorenopexy in patients with essential hypertension. The operation was performed on three patients aged twenty-four, thirty, and thirty-two years, respectively. The cut edge of the spleen was apposed to the cut surface of the kidney.

The results were uniform. In none of the patients with hypertension was the blood pressure reduced for more than three weeks. This patient was seriously ill at the time with pulmonary embolism and infarction. The other two showed a fall in blood pressure only during the operation.

It was concluded that splenorenopexy had no significant effect on the blood pressure of three patients with essential hypertension. NAIDE.

Pratt, G. H.: Traumatic Aneurysms of the Extremities. *Am. J. Surg.* 71:743 (June), 1946.

Five aneurysms of the lower extremities, the result of gunshot wounds, were present in 450 wounded men. A tendency to massive hemorrhage was characteristic and in itself was an indication for operation. As a result of the author's experience, the following suggestions were made relative to the management of such patients: Where possible, the operation should be postponed for three to six months to permit adequate collateral circulation to develop, but where the wound is open or infected, delay is dangerous. Operation in such instances should be performed at the earliest opportunity where adequate instruments and surgical personnel are available. Two tourniquets should accompany transportation of such patients and should be applied, in event of severe hemorrhage, above and below the site of bleeding. Sympathetic nerve blocks are an important part of therapy and may mean the difference between success and failure in the surgical treatment. Where plastic operation on the artery has been done, the anti-coagulants heparin and dicumarol are necessary and should be continued until the outcome is no longer in doubt. After operative recovery, these patients should be treated like those with obliterative arterial disease, with emphasis on the development of collateral circulation and care to prevent injury or infection of the part. NAIDE.

Blalock, A.: Effects of an Artificial Ductus Arteriosus on Experimental Cyanosis and Anoxemia. *Arch. Surg.* 52:247 (March), 1946.

Experimental studies were performed in an effort to determine whether the creation of an artificial ductus arteriosus would be helpful in the treatment of pulmonary stenosis or atresia in patients. Attempts to produce the desired degree of pulmonary stenosis were unsuccessful. It was then decided to attempt to produce unsaturation of the arterial blood by the removal of pulmonary tissue combined with the creation of a pulmonary arteriovenous fistula. This was finally done successfully by the removal of lobes of one or both lungs and the anastomosis of the severed proximal ends of the pulmonary artery and vein of these lobes. This resulted in a high degree of arterial oxygen unsaturation because some venous blood returned to the heart without having passed through pulmonary capillaries. An artificial ductus arteriosus was created by anastomosing the proximal end of the divided left subclavian artery to the side of the left pulmonary

artery in four of the experiments. In two dogs, the end of the innominate artery was anastomosed to the side of the right pulmonary artery. The creation of an artificial ductus arteriosus under these conditions usually resulted in an increase in the oxygen saturation of the arterial blood. The results of these studies strengthened the impression of Doctor Tausig that the patient with pulmonary stenosis would be improved if the pulmonary blood flow were increased and led to the development of the operation that is now performed on patients with pulmonary stenosis or atresia. NAIDE.

Gregory, R., Levin, W. C., Ross, G. T. and Bennett, A.: Studies on Hypertension: VI. Effect of Lowering the Blood Pressures of Hypertensive Patients by High Spinal Anesthesia on the Renal Function as Measured by Inulin and Diodrast Clearance. Arch. Int. Med. 77:385 (April), 1946.

The common therapeutic practice of attempting to lower the blood pressure of hypertensive patients made it advisable to determine whether such lowering of the blood pressure has any adverse influence. In view of the relationship of arterial pressure to renal filtration, the frequency with which hypertensive states are associated with pathologic changes, and the associated abnormalities which might influence arteriolar renal blood flow, it seemed especially desirable to determine whether therapeutically induced significant falls in blood pressure would affect renal function.

The methods used by these authors were as follows: inulin and diodrast clearances were determined as a control and after high spinal anesthesia was induced. This procedure was studied in ten patients with essential hypertension and in two patients with chronic glomerulonephritis. A significant fall in inulin and diodrast clearances was observed to occur in every instance in which the blood pressure fell significantly and remained low for as long as fifteen minutes. It was also observed that the degree of decrease in inulin and diodrast clearances was roughly proportional to the amount and duration of the fall of the blood pressure. That the decrease in clearance values was caused by the drop in blood pressure was shown by the following data: (1) The clearance values invariably rose toward the normal control levels during the second experimental hour when the blood pressure had risen toward or to the control level; (2) in several patients in whom the blood pressure remained low for two hours, the inulin and diodrast clearances remained proportionally low. In one patient in whom there was no fall in blood pressure although sensory paralysis had reached the second interspace, with complete motor paralysis of the lower extremities, there was a slight unexplained rise in pressure and a definite increase in clearance values.

The authors further emphasize that the correlation between the fall in blood pressure and the diminution in inulin and diodrast clearances occurs in patients with either normal or impaired renal function. They conclude that the results of this study necessitate a clinical appraisal of the effect on renal function of any therapeutic effort which aims at symptomatic lowering of the blood pressure in patients with hypertension. BELLET.

McDowall, R. J. S.: The Stimulating Action of Acetylcholine on the Heart. J. Physiol. 104:392 (April), 1946.

Acetylcholine injected into the isolated perfused hearts of cats, rabbits, and rats causes slowing and weakening of the heart beat which is almost invariably followed by an increase in rate and strength of the heart beat. Atropine abolishes the initial inhibitory effect of acetylcholine and, usually, the secondary acceleratory effect so that the only effect of acetylcholine after atropinization is a more forceable systolic contraction. Eserine enhances and ergotoxine abolishes or reverses the stimulating action of acetylcholine on the atropinized heart. After paralysis of the cardiac autonomic ganglia by nicotine, acetylcholine still exerts its stimulant effect; it must act, therefore, directly upon the cardiac muscle. After section of the A-V bundle, acetylcholine causes only a slight initial inhibitory effect upon the ventricle, followed by the usual stimulating effect.

On the basis of these data it is reasoned that the increased force of ventricular contraction during vagal slowing is not only a function of the cardiac muscle in accordance with Starling's Law of the Heart, but also a direct effect of the released acetylcholine on ventricular muscle. FRIEDLAND.

Book Reviews

ELECTROCARDIOGRAPHY: By Louis N. Katz, A.B., M.A., M.D., F.A.C.P. Lea & Febiger, Philadelphia, 1946, ed. 2.

This is the second edition of a well-known book and many obvious changes have been made in both text and illustrations. There are 825 pages with 525 excellent illustrations, a considerable increase over the previous edition. The paper stock is high grade and there are few, if any, typographical errors.

The author has changed his views on several subjects such as the range of the normal electrocardiogram and the nature of the shortened P-R, prolonged QRS syndrome. In the previous edition the precordial leads were limited to CF_2 and CF_4 , while this edition includes CF_5 .

Most beginners will find this book extremely complex, but an effort toward simplification has been made by listing the salient diagnostic points of each condition in concise fashion. Advanced students will find a wealth of material for study, although there may be a few controversial points which are treated according to the views of the author.

There are certain subjects which, while not of great importance, are inadequately treated. Because this is a comprehensive text, it seems unfortunate that short sections were not devoted to such subjects as an analysis of the various types of precordial leads and especially V leads. There is also inadequate discussion of extremity potentials and the esophageal lead.

Those who have used the first edition of this book will find the present edition familiar but with many improvements. Those who are unfamiliar with the work will find it a very satisfactory and comprehensive treatise. In a field which is expanding and changing as rapidly as electrocardiography, it is obviously a Herculean task to produce such a book. Readers will find it superior to most texts in this field.

SCOTT BUTTERWORTH.

EXERCISES IN ELECTROCARDIOGRAPHIC INTERPRETATION: By Louis N. Katz, A.B., M.A., M.D., F.A.C.P. Lea & Febiger, Philadelphia, 1946, ed. 2.

This book is a companion volume to the author's text on Electrocardiography. It includes 100 cases illustrated with 166 electrocardiograms and brief case histories. A number of new cases have been substituted in this edition and the total number of cases has been expanded from 90 to 100.

It is obviously difficult in selecting cases for a volume of this type to be comprehensive, but the author has selected a variety of types which cover the more common electrocardiographic variants and abnormalities, and he has wisely omitted complex or controversial cases. All of the electrocardiograms include Leads CF_2 and CF_4 in addition to the limb leads, and most also have CF_5 . An attempt has been made to include normal variants to illustrate the changes due to the position of the heart in the chest and other factors.

Embryo cardiologists will find this a very helpful book for training themselves in interpretation of "unknowns." More advanced students will find it a stimulating review which will allow them to study the views and interpretations of the author carefully.

SCOTT BUTTERWORTH.

American Heart Association, Inc.

1790 BROADWAY AT 58TH STREET, NEW YORK, N. Y.

DR. ROY W. SCOTT
President

DR. HOWARD F. WLST
Vice-President

DR. GEORGE R. HERRMANN
Treasurer

DR. HOWARD B. SPRAGUE
Secretary

BOARD OF DIRECTORS

DR. EDGAR V. ALLEN . . .	Rochester, Minn.	DR. HAROLD E. B. PADDLE . . .	New York City
DR. GRAHAM ASHUR . . .	Kansas City, Mo.	DR. WILLIAM H. PORTER . . .	Richmond, Va.
*DR. ARTHUR R. BARNES . . .	Rochester, Minn.	*DR. DAVID D. RUTSTEIN . . .	New York City
DR. ALFRED BLALOCK . . .	Baltimore	*DR. JOHN J. SAMPSON . . .	San Francisco
*DR. WILLIAM H. BUNN . . .	Youngstown, Ohio	DR. ROY W. SCOTT . . .	Cleveland
DR. CLARENCE DE LA CHAPLLE . . .	New York City	*DR. HOWARD B. SPRAGUE . . .	Boston
*DR. TINSLEY R. HARRISON . . .	Dallas	DR. GEORGE F. STRONG . . .	Vancouver, B. C., Can.
DR. GEORGE R. HERRMANN . . .	Galveston	DR. WILLIAM D. STROUD . . .	Philadelphia
DR. T. DUCKETT JONES . . .	Boston	DR. HOMER F. SWIFT . . .	New York City
DR. LOUIS N. KATZ . . .	Chicago	DR. WILLIAM P. THOMPSON . . .	Los Angeles
DR. SAMUEL A. LEVINE . . .	Boston	DR. HARRY E. UNGERLEIDER . . .	New York City
DR. GILBERT MARQUARDT . . .	Chicago	*DR. HOWARD F. WLST . . .	Los Angeles
*DR. H. M. MARVIN . . .	New Haven	DR. PAUL D. WHITE . . .	Boston
*DR. EDWIN P. MAYNARD, JR. . .	Brooklyn	DR. FRANK N. WILSON . . .	Ann Arbor
*DR. THOMAS M. McMILLAN . . .	Philadelphia	*DR. IRVING S. WRIGHT . . .	New York City
DR. JONATHAN MAKINS . . .	Montreal, Can.	DR. WALLACE M. YATTE . . .	Washington, D. C.
DR. E. STERLING NICHOL . . .	Miami		

*Executive Committee.

DR. H. M. MARVIN, *Acting Executive Secretary*

ANNA S. WRIGHT, *Office Secretary*

Telephone, Circle 5-8000

THE American Heart Association is the only national organization devoted to educational work relating to diseases of the heart. Its activities are under the control and guidance of a Board of Directors composed of thirty-three eminent physicians who represent every portion of the country.

A central office is maintained for the coordination and distribution of important information. From it there issues a steady stream of books, pamphlets, charts, films, lantern slides, and similar educational material concerned with the recognition, prevention, or treatment of diseases of the heart, which are now the leading cause of death in the United States. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning the circulation of blood and lymph. Any physician or investigator may become a member of the section after election to the American Heart Association and payment of dues to that organization.

The income from membership and donations provides the sole financial support of the Association. Lack of adequate funds seriously hampers more intensive educational activity and the support of important investigative work.

Annual membership is \$5.00. Journal membership at \$11.00 includes a year's subscription to the AMERICAN HEART JOURNAL (January-December) and annual membership in the Association. The Journal alone is \$10.00 per year.

The Association earnestly solicits your support and suggestions for its work. Membership application blanks will be sent on request. Donations will be gratefully received and promptly acknowledged.

American Heart Journal

VOL. 32

OCTOBER, 1946

No. 4

Original Communications

THE RELATION BETWEEN CIRCULATION TIME AND THE AMOUNT OF THE RESIDUAL BLOOD OF THE HEART

B. GERNANDT, M.D., AND G. NYLIN, M.D.

STOCKHOLM, SWEDEN

THE introduction of determinations of circulation times has afforded the clinician assistance in diagnosis, prognosis, and management. A number of important studies have been published on this subject. Blumgart and Weiss¹ injected radium C intravenously and, with Geiger-Müller tubes, were able to determine the time when the injected substance arrived in different parts of the vascular system. The advantage of this method was that an objective determination of the time interval was obtained. Weiss was able to demonstrate a retardation, as compared with the normal, in patients with cardiovascular disease. In cases of cardiac insufficiency, it was observed that the protraction of the circulation time was, to a certain extent, proportional to the degree of insufficiency.

Winternitz and his co-workers² injected sodium aurodecholate into the vena cubiti and determined the time required for the patient to notice a bitter taste on his tongue. In spite of the fact that the patient's subjective cooperation is necessary, the inaccuracy of this method is surprisingly small, as results which were in very good agreement were obtained in repeated experiments on the same patient.

Employing Winternitz's method, Tarr, Oppenheimer, and Sager³ found the normal circulation time to be 10 to 16 seconds with a mean value of 13 seconds, reckoning from the instant when the injection was given until the patient noticed the first taste sensation. For "compensated heart patients," Tarr found a moderate prolongation of the circulation time, and for the "decompensated patients" he found a considerable prolongation.

From Medical Department II, the Sabbatsberg Hospital, Stockholm. Chief: Docent G. Nylin, M.D.

Received for publication Jan. 25, 1946.

Malmström and Nylin,⁴ using decholin in 48 healthy persons, found that the first taste sensation appeared after 8 to 21 seconds; the mean value was 12 seconds. The sensation persisted for periods varying from 7 to 24 seconds, the mean being 12.8 seconds. The authors observed a decided relation between the circulation time and the size of the heart (measured in accordance with the method of Nylin, Lysholm, and co-workers¹³) in patients with compensated cardiovascular disease.

Nylin^{5,6} earlier observed that the heart is subjected to considerable sudden volume changes both under physiologic and pathologic conditions, and that these acute volume changes are due to variations in the amount of the residual blood. He pointed out also that the circulation time is not only dependent on the degree of insufficiency, but is also largely determined by the amount of the residual blood. He found, too, that the heart volume is considerably larger in the recumbent position than in an upright position, owing to the amount of the residual blood. Simultaneously with this change in heart volume, Malmström and Nylin⁴ observed a prolongation of the circulation time in the recumbent position in comparison with that in the upright position.

Nylin⁷⁻¹⁰ employed G. de Hevesy's method of labeling red blood corpuscles and applied this method to the problem of the circulation time and the amount of the residual blood. These investigations show that, however subjective the method may be, the decholin method agrees on the whole with the objective method in which labeled red blood corpuscles are used.

In the present study a more thorough investigation has been made of the prolongation of the circulation time in the dilated heart due to the increased amount of residual blood. In particular, the connection between the circulation time and the heart volume has been studied, and the results have been handled statistically.

The studies of Nylin and his co-workers have proved clearly that, above all, the circulation time depends on the amount of the residual blood in the heart, and only to a slight extent on the degree of decompensation, i.e., of congestion. This relationship has not been pointed out previously. The establishment of this connection between circulation time and the amount of the residual blood is not only of theoretical but also of important practical interest. Thus, it is necessary to pay due attention to the varying amounts of residual blood in determinations of the blood volume, and perhaps also in other investigations of the blood flow.

The determination of the circulation time affords a possible method of determining in a simple way whether or not the heart is dilated.

METHOD

Determinations of the circulation time and venous pressure were made on patients under resting conditions. The patient, the upper part of whose body was bare, lay flat on his back on a bed from which the pillows had been removed. A cannula with an inside diameter of 0.9 mm. was inserted into a cubital vein. The cannula, which was heparinized, was connected with a fitting, in which an

upright manometer tube was fixed. The measurement of the venous pressure was made when the injection needle was on a level with the central axillary line. By means of slight pressure with the hand around the patient's arm above the cannula one could easily make sure whether the venous pressure rose when the arm was compressed and fell when the pressure was relaxed, and that there was a free connection. Into the fitting, which was constructed as a three-way tap, an injection syringe could be connected. By turning the three-way tap, the injection syringe could be connected to the cannula.

In determinations of circulation times, 5 ml. of a 20 per cent decholin solution was injected as quickly as possible. The time was taken from the instant the syringe plunger reached the bottom. The patient then had to indicate when he first perceived the sensation of a bitter taste, when it began to recede, and when it had disappeared entirely.

The method has been previously described in detail and critically discussed by Malmström and Nylin.⁴

The determinations of the heart volume were made in accordance with the method worked out by Lysholm, Nylin, and co-workers.^{12,13} In healthy persons, according to these authors, the normal mean value of the absolute heart volume (V) is 700 c.c. with a range of 457 to 945 cubic centimeters. The relative heart volume ($V/M.^2$), i.e., the volume expressed in cubic centimeters per square meter of body surface, is, on the average, 370 c.c. with a range of 250 to 490 cubic centimeters.

PRESENT INVESTIGATIONS

The material, which comprised 308 patients with heart disease, was divided into "compensated" and "decompensated" cases. The presence of decompensation was determined by general signs of congestion, such as palpable liver, palpable spleen, edema, roentgenologically demonstrable lung congestion. Roentgenologic determinations of the heart volume, determinations of the circulation time, and measurements of the venous pressure were made on every patient.

Table I is a summary of the material, with calculations of the mean, standard error of the mean, standard deviation, and coefficient of variation.

There is a clear correlation between both the absolute (V) and the relative ($V/M.^2$) heart volume and the circulation time, with a correlation coefficient of 0.51 and 0.50, respectively (Table II and Fig. 1). There does not appear to be any definite connection between the heart volume or heart volume per square meter of body surface and the venous pressure, as appears from the low correlation coefficients shown in Table II. From Fig. 2 it is clear that, when the heart volume increases from 350 to 900 c.c. per square meter of body surface in the compensated cases, the rise in venous pressure is extremely slight. Consequently, the conclusion may be drawn that the circulation time is determined chiefly by the heart volume, and therefore by the amount of the residual blood, and to a lesser degree by the height of the venous pressure in the case of compensated heart disease. If a comparison is made of the relation between the absolute heart volume

TABLE I. THE HEART VOLUME, HEART VOLUME PER SQUARE METER OF BODY SURFACE, VENOUS PRESSURE, AND CIRCULATION TIME IN CASES OF COMPENSATED AND DECOMPENSATED HEART DISEASE

	NUMBER	M	$\pm \sigma_m$	S. D.	$V = \frac{100 \text{ S.D.}}{M}$
<i>Compensated:</i>					
Heart volume in cubic centimeters (V).	214	987.6	± 23.3	± 340.3	34.5
Heart volume in relation to the estimated body surface (V/M. ²).....	202	568.7	± 13.9	± 197.3	34.7
Circulation time in seconds (first taste sensation).....	214	18.68	± 0.53	± 7.68	41.1
Venous pressure in centimeters.....	213	8.97	± 0.23	± 3.39	37.8
<i>Decompensated:</i>					
Heart volume in cubic centimeters (V).	94	1,437.2	± 55.3	± 536.3	37.4
Heart volume in relation to the estimated body surface (V/M. ²).....	93	832.5	± 32.8	± 316.3	38.0
Circulation time in seconds (first taste sensation).....	94	27.68	± 1.27	± 12.30	43.4
Venous pressure in centimeters.....	94	18.10	± 0.65	± 6.32	35.0

TABLE II. THE RELATION BETWEEN THE HEART VOLUME IN CUBIC CENTIMETERS AND THE CIRCULATION TIME (THE FIRST TASTE SENSATION) IN SECONDS AND BETWEEN THE HEART VOLUME AND THE VENOUS PRESSURE IN CENTIMETERS IN CASES OF COMPENSATED HEART DISEASE

CORRELATION	NUMBER	$r \pm \sigma_r$
<i>Compensated:</i>		
Volume (V)—circulation time.....	214	0.51 \pm 0.051
Volume (V)—venous pressure.....	213	0.16 \pm 0.067
Volume (V/M. ²)—circulation time.....	202	0.50 \pm 0.053
Volume (V/M. ²)—venous pressure.....	201	0.15 \pm 0.069
Circulation time—venous pressure.....	213	0.18 \pm 0.066

and the time from the moment of the injection to the last taste sensation instead of, as before, to the first taste sensation, a correlation coefficient of 0.40 is found (Table III), which indicates that here, too, there is a relation between the amount of the residual blood and the length of the circulation time (determined by the cessation of the taste sensation) in the compensated cases.

TABLE III. THE RELATION BETWEEN THE ABSOLUTE HEART VOLUME AND THE CIRCULATION TIME* AND BETWEEN THE ABSOLUTE HEART VOLUME AND THE DURATION OF THE TASTE SENSATION†

CORRELATION	NUMBER	$r \pm \sigma_r$
Heart volume (V)—circulation time (last value).....	198	+0.40 \pm 0.060
Heart volume (V)—difference in circulation time.....	198	+0.27 \pm 0.066

*The time from the moment of the injection to the disappearance of the bitter taste.

†The time between the first and last taste sensations.

In the decompensated heart cases, there is a clear correlation between both the absolute (V) and the relative (V/M.²) heart volume and the circulation time, although it is less pronounced than in the compensated cases. The correlation coefficients are 0.45 and 0.37 (Table IV and Fig. 1). This correlation is, however, greater in reality than appears from the correlation coefficient, as the line which represents the correlation is curved (Fig. 1).

TABLE IV. THE RELATION BETWEEN THE HEART VOLUME IN CUBIC CENTIMETERS AND THE CIRCULATION TIME (FIRST TASTE SENSATION) IN SECONDS, AND BETWEEN THE HEART VOLUME AND VENOUS PRESSURE IN CASES OF DECOMPENSATED HEART DISEASE

CORRELATION	NUMBER	$r \pm \sigma_r$
<i>Decompensated:</i>		
Volume, rtg.* (V)—circulation time.....	94	0.45 ± 0.082
Volume, rtg. (V)—venous pressure.....	94	0.36 ± 0.090
Volume, rtg. (V/M. ²)—circulation time.....	93	0.37 ± 0.090
Volume, rtg. (V/M. ²)—venous pressure.....	93	0.37 ± 0.090
Circulation time—venous pressure.....	94	0.39 ± 0.088

*Rtg.=roentgenologic.

In comparison with cases of compensated heart disease, there is in cases of decompensated heart disease a closer relation between the heart volume and the venous pressure, as appears from the relatively high correlation coefficient of 0.37 (Table IV and Fig. 2).

TABLE V. THE CORRELATION BETWEEN THE ABSOLUTE HEART VOLUME AND THE CIRCULATION TIME* AND BETWEEN THE ABSOLUTE HEART VOLUME AND THE DURATION OF THE TASTE SENSATION†

CORRELATION	NUMBER	$r \pm \sigma_r$
<i>Decompensated:</i>		
Volume (V)—circulation time (last value)....	78	$+0.42 \pm 0.093$
Volume (V)—difference in circulation time....	78	$+0.21 \pm 0.108$

*The time from the moment of injection to the disappearance of the bitter taste.

†The time between the first and last taste sensations in cases of decompensated heart disease.

As in the compensated cases, there is also in the decompensated cases an obvious correlation between the absolute heart volume and the time interval between the moment of injection and the last taste sensation, with a correlation coefficient of 0.42 (Table V). The duration of the taste sensation only gives a correlation coefficient of 0.21.

SUMMARY

A statistical investigation on a considerable number of patients with both compensated and decompensated heart disease as to the relation between the size of the heart, the heart volume determined roentgenologically, and the circulation time gives the following results:

In both compensated and decompensated heart disease there is a statistically verified correlation between the heart volume, i.e., the amount of the residual blood, and the circulation time (first taste sensation). There is a similar correlation between the heart volume and the circulation time (the last taste sensation). The explanation of these two circumstances, which were first observed by Nylin, is found if it is assumed that the greater the amount of the residual blood in the heart the longer time it takes for the test substance injected to become mixed with the residual blood and to reach the peripheral arterial system. Similarly, the late disappearance of the bitter taste is explained by the fact that it takes longer for the heart to pump out the test substance when the amount of the residual blood is large, as in cases of dilated hearts.

These statistical results are in complete accord with Nylin's experiences in determining the circulation times by means of radioactive phosphorus.

The authors wish to express their gratitude to Professor G. Dahlberg of the Race Biological Institute at Upsala for his kind assistance with the statistical studies.

REFERENCES

1. a. Blumgart, H. L., and Weiss, S.: Studies on Velocity of Blood Flow; Velocity of Blood Flow in Normal Resting Individuals, and Critique of Method Used, *J. Clin. Investigation* 4: 15, 1927.
 b. Idem: Studies on Velocity of Blood Flow; Physiological and Pathological Significance of Blood Flow, *J. Clin. Investigation* 4: 199, 1927.
 c. Idem: Studies on Velocity of Blood Flow; Method of Collecting Active Deposits of Radium and Its Preparation for Intravenous Injection, *J. Clin. Investigation* 4: 389, 1927.
 d. Idem: Clinical Studies on Velocity of Blood Flow; Pulmonary Circulation Time, Velocity of Venous Blood Flow to Heart, and Related Aspects of the Circulation in Patients With Cardiovascular Disease, *J. Clin. Investigation* 5: 343, 1928.
 e. Idem: Clinical Studies on Velocity of Blood Flow, Venous Pressure and Vital Capacity of Lungs in 50 Patients With Cardiovascular Disease Compared With Similar Measurements in 50 Normal Persons, *J. Clin. Investigation* 5: 379, 1928.
 f. Idem: Clinical Studies on Velocity of Blood Flow; Pulmonary Circulation Time, Minute Volume Blood Flow Through Lungs, and Quantity of Blood in Lungs, *J. Clin. Investigation* 6: 103, 1928.
 g. Idem: Studies on Velocity of Blood Flow; Circulation in Myxedema With Comparison of Velocity of Blood Flow in Myxedema and Thyrotoxicosis, *J. Clin. Investigation* 9: 91, 1930.
2. Winternitz, M., Deutsch, J., and Brüll, Z.: Eine Klinisch brauchbare Bestimmungsmethode der Blutumschlagszeit mittels Decholininjektion. (Kurze Mitteilung), *Med. Klin.* 27: 986, 1931.
3. Tarr, L., Oppenheimer, B. S., and Sager, R. V.: The Circulation Time in Various Clinical Conditions Determined by the Use of Sodium Dehydrocholate, *Am. Heart J.* 8: 766, 1933.
4. Malström, G., and Nylin, G.: Weitere Untersuchungen über die Bedeutung der verlängerten Kreislaufzeit für die Kardiologie, *Cardiologia* 5: 333, 1942.
5. Nylin, G., Sällström, T., and Agren, O.: Physiologische und pathologische Herzvolumenschwankungen, *Verhandl. d. deutsch. Gesellsch. f. Kreislaufforsch.* 12: 369, 1939.
6. Nylin, G.: Relation Between Heart Volume in Recumbent and Erect Positions, *Skandinav. Arch. f. Physiol.* 69: 237, 1934.
7. a. Nylin, G., and Malm, M.: Ueber die Konzentration von mit radioaktivem Phosphor markierten Erythrocyten im Arterienblut nach der Intravenösen Injektion solcher Blutkörperchen, *Cardiologia* 7: 153, 1943.
 b. Nylin, G., and Malm, M.: Concentration of Red Blood Corpuscles Containing Labeled Phosphorus Compounds in Arterial Blood After Intravenous Injection; Preliminary Report, *Am. J. M. Sc.* 207: 743, 1944.

8. Nylin, G.: The Dilution Curve of Activity in Arterial Blood After Intravenous Injection of Labeled Corpuscles, *AM. HEART J.* 30: 1, 1945.
9. Nylin, G.: Blood Volume Determinations With Radioactive Phosphorus, *Brit. Heart J.* 7: 81, 1945.
10. Nylin, G.: *Arkiv för kemi, mineralogi och geologi*, Bd. 20 A, Nr. 17, sid. 1, 1945. (Kungl. Vetenskapsakademien.)
11. Nylin, G.: On the Amount of, and Changes in, the Residual Blood of the Heart, *AM. HEART J.* 25: 598, 1943.
12. Lysholm, E., Nylin, G., and Quarna, K.: Relation Between Heart Volume and Stroke Volume Under Physiological and Pathological Conditions, *Acta radiol.* 15: 237, 1934.
13. Liljestrand, G., Lysholm, E., Nylin, G., and Zachrisson, C. G.: The Normal Heart Volume in Man, *AM. HEART J.* 17: 406, 1939.

THE HEART IN PRIMARY SYSTEMIC AMYLOIDOSIS

STUART LINDSAY, M.D.

SAN FRANCISCO, CALIF.

THERE is a large group of uncommon diseases, some systemic in nature, in which involvement of the heart may lead to cardiac failure.³⁸ Few of these^{39,40} have been so delineated that their clinical, laboratory, and pathologic sequences differentiate them easily from the more common types of cardiac disease. By observation of certain peculiarities of their manifestations, and by the recognition of the basic process or lesions in other tissues, one is not likely to overlook the significance of certain of these generalized diseases which may be accompanied by cardiac signs and symptoms.

Amyloidosis, particularly the primary systemic form of the disease, constitutes one member of this group of miscellaneous, obscure cardiac diseases. Weiss and co-workers⁴⁰ have pointed out that an accurate etiologic classification of these rare types of disease is mandatory, mainly because of the practical importance of specific therapy. While no patients with primary amyloidosis have recovered, none has received a form of therapy which appears to be efficacious in the secondary type of amyloidosis.^{41,67}

The purpose of the present report is (1) to summarize the clinical and pathologic data available in the published reports of over forty cases of primary systemic amyloidosis from the standpoint of clinical cardiac and systemic manifestations, aids in diagnosis, electrocardiographic records, and pathologic changes in cardiac tissues; and (2) to record an additional case of primary amyloidosis in which extensive, diffuse, myocardial, amyloid infiltration was responsible for progressive cardiac failure and death.

CASE REPORT

First Admission.—A. S., —U47646, a married white woman, 59 years of age, the wife of a clergyman, first entered the hospital on July 6, 1939.

Clinical History: For six months before entry she had noted increasing exertional dyspnea and weakness. Three months before, edema of the ankles occurring at the end of the day appeared. Three days before, she had first noticed substernal pain following moderate exertion. An electrocardiogram, done four months before entry, showed a very low voltage and a moderate left-axis deviation. Family and past history contained several significant items. Her father died at the age of 72 years of peptic ulcer. Her mother's death at the age of 75 years was due to a cerebrovascular accident. The patient had two spontaneous abortions at two and three months. The first was followed by an attack of "rheumatism," which was relieved by uterine curettage.

From the Division of Pathology, University of California Medical School.
Received for publication March 4, 1946.

Migraine headaches, precipitated by the ingestion of eggs, had occurred since childhood. Her three children had similar headaches. One year before, mild enlargement and pain in the knees and small joints of the hands occurred. These articular symptoms had persisted but were stationary.

Physical Examination: The patient was an asthenic, well-nourished white woman. The temperature was 37.4°C.; pulse rate, 90; respiratory rate, 24; weight, 53.6 kilograms (118 pounds). The head, eyes, ears, nose, and mouth were normal. When she was in the sitting position, the cervical veins were distended to a point 12 cm. above the second interspace. The left border of the heart was 1.5 cm. to the left of the mid-clavicular line. There was no enlargement to the right. A soft systolic murmur of moderate intensity could be heard at the mitral and aortic areas. The aortic second sound was hollow. There were occasional ventricular extrasystoles. The blood pressure was 95/60. The lungs were clear throughout. Examination of the abdomen, back, rectum, genitals, and nervous system showed nothing abnormal. There were obvious varicose veins and slight pitting edema of both lower extremities. The interphalangeal joints of both hands were slightly widened, without any limitation of motion. Fluoroscopy of the chest showed a diffuse enlargement of the heart, involving mainly the left ventricle and auricle. The right side of the heart was enlarged to a lesser extent. The cardiac contractions were poor, and, at the apex of the left ventricle, were almost absent. The bronchovascular markings near the hilum of each lung were widened.

Laboratory Examination: Examination of the blood gave the following data: hemoglobin, 85 per cent (12.3 Gm.); red blood cells, 4.5 million; white blood cells, 10,100, polymorphonuclear leucocytes, 58.5 per cent (filamented, 48.5 per cent; nonfilamented, 10 per cent); eosinophiles, 2 per cent; basophiles, 0.5 per cent, lymphocytes, 32 per cent, monocytes, 7 per cent. The erythrocytes and platelets were normal. The sedimentation rate (Wintrobe) was 17 mm. (cell volume, 44 c.c. per cent; corrected rate, 20 mm.). Blood serum proteins: albumin, 3.61 per cent; globulin, 1.90 per cent; albumin-globulin ratio, 1.9. The urine contained a slight trace of albumin. Tests for urobilin and urobilinogen were positive in undiluted urine but were negative in dilutions of 1:20. No serologic tests for syphilis were done.

Gastric analysis with histamine showed a level of free hydrochloric acid reaching 48 degrees, with the total acidity reaching 64 degrees. Pepsin and rennin were present in the gastric juice. The basal metabolic rate was -4 per cent.

A clinical diagnosis of congestive cardiac failure due to coronary arteriosclerosis was made. The patient's course was uneventful. She was advised to continue at home a regime of bed rests, Galen B (the vitamin B complex from rice polishings), a high protein diet, and digitalis.

Second Admission.—The patient's second entry was on August 17, 1939. One week before admission an acute upper respiratory infection with pain in the legs and back occurred. Shortly thereafter she developed pain in the right lower chest, accentuated by respiratory movements. Increasing dyspnea, palpitation, and slight cough and a temperature of 38.8°C. appeared. There was a slight increase in peripheral edema. These symptoms and findings were less severe at the time of entry into the hospital.

On admission, physical signs of a right pleural effusion were found, and 500 c.c. of sero-sanguineous fluid were removed from the right pleural cavity. Its specific gravity was 1.016 and the Rivalta test was positive. No bacteria were present, and the sediment contained only mesothelial and red and white blood cells. The heart was still enlarged. The heart sounds were the same as on previous examination. The cardiac rhythm was regular; the rate was 90.

Laboratory Examination: Examination of the blood gave the following data: hemoglobin, 86 per cent (12.5 Gm.); erythrocytes, 4.25 million; leucocytes, 9,900; polymorphonuclear leucocytes, 55.5 per cent (filamented, 47.5 per cent; nonfilamented, 8 per cent); eosinophiles, 3 per cent; basophiles, 0; lymphocytes, 31.5 per cent; monocytes, 10 per cent. The erythrocytes and platelets were normal. Observed sedimentation rate, 37 mm. (cell volume, 41 c.c. per cent; corrected rate, 34 mm.). The urine contained a moderate amount of albumin. Tests for urobilin and urobilinogen were positive in an undiluted specimen but were negative at 1:20 dilution. Blood serum proteins: total, 6.4 mg. per cent; albumin, 4.08 mg. per cent; globulin, 2.32 mg. per cent;

albumin-globulin ratio, 1.76. An electrocardiogram showed a rate of 93, ventricular premature systoles, slight left-axis deviation, low-voltage QRS complexes, and low T waves in Leads I and II (Fig. 1).

During the next twenty-six days, the amount of fluid in the right pleural cavity continued to decrease. The sedimentation rate dropped to 27 mm. Despite almost complete bed rest and a maintenance dose of digitalis of 1 dg. per day, the cardiac rate remained at about 90. Four intravenous mercurial injections produced a good diuresis and prevented a gain in weight. The intake of fluids and salt was restricted.

Third Admission.—The last entry in the hospital was on Nov. 13, 1939. While at home, the patient had not improved and had been bedridden. Six days before admission, the dyspnea had increased. She had noted a constricting sensation in the thorax, with severe inspiratory, bilateral thoracic pain. She became orthopneic and developed a low-grade fever. Four days before admission, she became nauseated and began to vomit. Swelling of the face had been present for some time but was more pronounced shortly before entering the hospital.

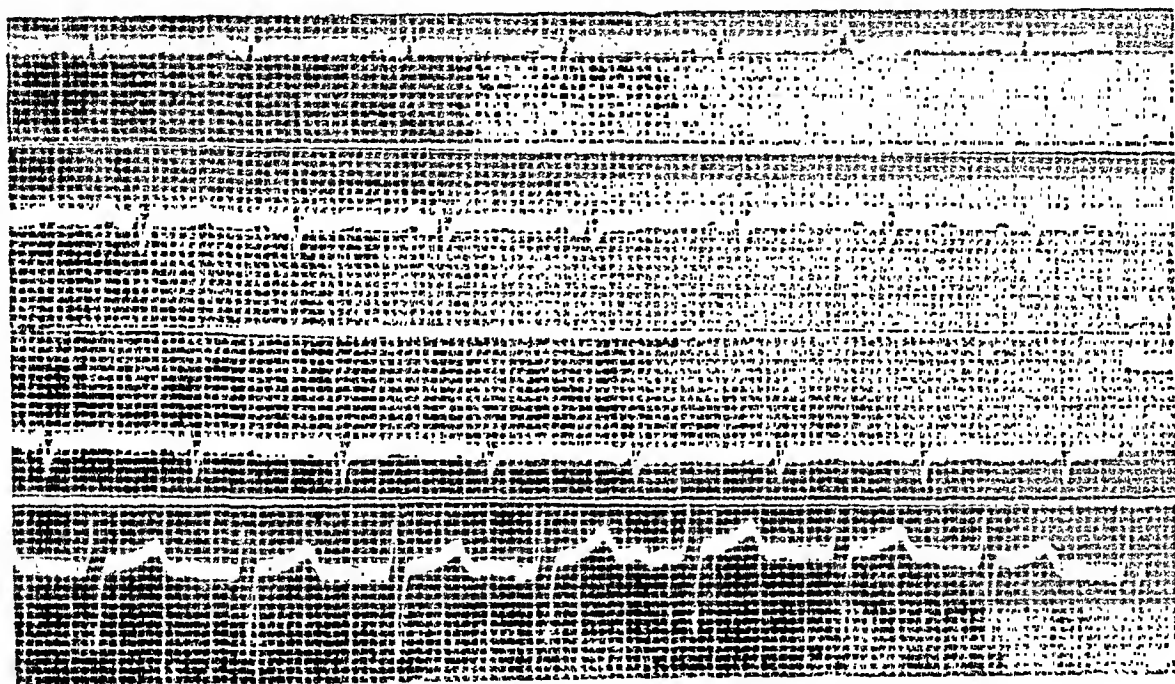


Fig. 1.—Electrocardiogram made on Aug. 1, 1939.

Physical Examination: The temperature was 38° C.; pulse rate, 90; respiratory rate, 26. The patient was orthopneic and slightly cyanotic. There was edema of the face and ankles. Abnormal venous distention of the neck was noted. The chest expanded poorly and there were physical signs of fluid in both pleural cavities. The heart was enlarged to the left in the fifth intercostal space. The sounds were poor. A gallop rhythm was heard at the apex, and a systolic murmur was heard at the aortic area. The blood pressure was 90/75. There was guarding in the upper right quadrant of the abdomen and the liver was enlarged. Edema of the ankles and sacral region was present.

Laboratory Examination: Examination of the blood gave the following data: hemoglobin, 88 per cent (12.8 Gm.); red blood cells, 4.62 million; white blood cells, 12,600; polymorphonuclear leucocytes, 65 per cent; lymphocytes, 25 per cent; monocytes, 10 per cent. The erythrocytes and platelets were normal. The feces were normal. An electrocardiogram showed a rate of 100 per minute, low voltage of the QRS complex, left-axis deviation, low T₁, T₂, T₃, and T₄, slight elevations of S-T₄, and a small R₄.

Courses: Removal of 700 c.c. of fluid from the right pleural cavity produced little change in the patient's condition which remained poor during the next two weeks. She had frequent attacks of migraine with nausea and abdominal distention. The heart sounds had a poor quality; there was a gallop rhythm with occasional ventricular extrasystoles. The rate continued at 100. The cervical veins were distended and pulsating, and hepatic enlargement was progressing. Bilateral hydrothorax and edema of the face and legs were not relieved by mercurial injections and aminophylline. During this period, lumbar puncture showed clear cerebro-spinal fluid, containing eight lymphocytes per cubic millimeter. The initial pressure was 180 mm. of water, and the Pandy, Lange, and Kahn tests gave normal findings.

On Nov. 30, 1939, the patient became stuporous and was found to have a left flaccid hemiplegia. Within the next few days the deep reflexes on the left side returned and she became more responsive. During the following three weeks, the muscular tone and voluntary movements on the left side increased, though she remained confused and disoriented, and had considerable difficulty in speech.

The cardiac status slowly became worse. Pulmonary congestion became more pronounced. The pulse rate varied between 110 and 130, and the respiratory rate, between 25 and 35. Several episodes of Cheyne-Stokes breathing responded to aminophylline. During the last three weeks of life, there was a gradual elevation of temperature to a terminal level of 40.4° C. The edema of the arms and legs was much more pronounced on the left hemiplegic side of the body for two days before death. This difference had no relation to position in bed. Death from cardiac failure occurred on Jan. 11, 1940, approximately one year following the onset of cardiac symptoms.

Autopsy Report.—The autopsy (UA 40.5) was performed one and one-half hours after death. There was marked wasting of the subcutaneous fat and musculature. The temporal and cervical veins were distended and tortuous. The abdomen was distended. There was edema of both legs and arms, greater on the left side. The inter-phalangeal joints of the hands were slightly enlarged. The surface of the skin, the eyes, ears, nose, and mouth were normal.

The peritoneal cavity and each pleural cavity contained 1,000 c.c. of clear yellow fluid. The heart was enlarged. The left border extended 11 cm. to the left of the midline and the right border 5 cm. to the right of the midline. Dense bilateral pleural fibrous adhesions were present. The heart weighed 500 Gm. The serosal surfaces were smooth and glistening and had normally distributed pericardial fat. All of the cardiac chambers were moderately dilated. There was anatomic patency of the foramen ovale. The ventricular walls were hypertrophied, with the left averaging 2.3 cm. in thickness and the right, 1.3 cm. in thickness. The auricular walls varied between 0.2 and 0.6 cm. in thickness. All portions of the myocardium were unusually firm and stiff; the auricular walls had a leathery consistency. There was a pale brownish-tan pallor of the entire myocardium. Throughout this layer, including the interventricular septum, trabeculae carneae, and ventricular papillary muscles, was a diffuse network of pale grayish-yellow, translucent material, tending to be concentrated about visible blood vessels and within the interstitial tissues. Strong solution of iodine (U. S. P.) stained the myocardium diffusely, producing a mahogany-brown color, with the translucent areas taking the stain more deeply (Fig. 2). The amyloid infiltration was most abundant in the left ventricular wall. Less abundant infiltration had occurred in the epicardial fat. The cardiac valves were not grossly altered. There was a mild translucent intimal thickening of the main coronary arteries, but these vessels had widely patent lumens, and no atheromatous lesions were present. No nodular amyloid deposits were encountered in the heart. Both auricular appendages contained adherent ante-mortem thrombi.

The right lung weighed 300 grams and the left lung weighed 340 grams. Both lungs were partially atelectatic and mildly congested and edematous. The cut surfaces had a pale, pink, glistening, moist appearance, and a rubbery consistency.

The liver weighed 1,080 grams. Its parenchyma was brown in color, and there was moderate central lobular congestion. A 1 cm. cavernous hemangioma lay beneath the capsular surface of the right lobe. The gall bladder was distended with bile, but its wall was normal. The spleen weighed 70 grams and its capsule was smooth. The splenic pulp was firm, dark purple in color, and was not hyperplastic. Scattered throughout were small 1 to 2 mm. zones of translucent, soft, amyloid material. The pulp stained diffusely with strong solution of iodine (U. S. P.). The discrete amyloid masses stained a deeper brown.

Except for loss of distinct corticomedullary differentiation, the kidneys were normal. The pancreas and adrenal glands were grossly normal.

The ovaries, Fallopian tubes, and uterus were atrophic. The uterine canal was lined by a thin, pale, smooth endometrial layer. There was an unusual glistening pallor and translucency of the inner half of the myometrial layer.



Fig. 2.—Section of heart showing diffuse amyloid infiltration of myocardium and less abundant deposition in the epicardium and endocardium ($\times 4/5$). Stained with strong solution of iodine (U. S. P.) followed by acidified Eastman x-ray fixer. Photographed with red Wratten B filter No. 25.

Almost the entire muscular layer of the stomach, especially of the pyloric end, was thickened, firm, and rubbery. Extensive deposits of pale yellowish-gray, translucent amyloid material lay between isolated muscle bundles. This muscular alteration was particularly marked in and just above the pyloric sphincter. On the surface, the amyloid deposits appeared as longitudinal ridges and cords, visible through the transparent serosal layer. There was no gross evidence of amyloid infiltration of the large and small bowel, but the outer muscular layer of the lower esophagus showed changes similar to those seen in the stomach. After fixation for several days in a solution of formaldehyde (U. S. P.), the gastroenteric amyloid took on a brownish-purple color but retained its shining, translucent characteristics. The cardiac amyloid did not show this alteration.

The bone marrow of the lumbar spine was normal. A few small atheromatous plaques were present in the intima of the aorta. There was no gross alteration of the superior or inferior vena cava.

The entire right frontal lobe of the brain was pale, flattened, and soft. On section, this frontal lobe, with the underlying basal nuclei, was almost entirely liquified. The superficial layer of the cortex was relatively intact. The right anterior and right middle cerebral arteries

and the left carotid artery were occluded by ante-mortem thrombi. The pituitary and thyroid glands were normal.

Microscopic Descriptions: The walls of both ventricles of the heart had a similar histologic appearance. Many of the fat cells of the subendocardial layer had thickened eosinophilic cell membranes, which gave positive staining reactions for amyloid. All layers of the main coronary arteries and the medium-sized arteries and veins in this layer were moderately infiltrated with homogeneous eosinophilic amyloid material.

There was diffuse intercellular amyloid deposition in the myocardium (Fig. 3). The material lay between individual muscular cells and was continuous with amyloid infiltrating the adventitia of blood vessels and that surrounding the endothelial wall of small capillaries. When seen in cross section, each myocardial fiber was encased in an amyloid ring, producing a honey-comb appearance. The amount of intercellular amyloid varied in different parts of the myocardium. Where it was most abundant, the enclosed myocardial fibers were compressed, atrophied, granular, and degenerating. The nuclei were distorted. Some fibers had disappeared, leaving fusiform spaces in the amyloid matrix. Other fibers were absent, leaving amyloid rings which occasionally contained small clumps of eosinophilic debris and golden-brown pigment. Some areas showed large amyloid sheets with no residual myocardial fibers. Elsewhere in the interstitial tissue were nodular, small, rounded amyloid deposits. Small lipid globules in many of the degenerating muscle cells were revealed with the sudan IV stain. For the most part, the interstitial amyloid was homogeneous, compact, refractile; in some areas it was frayed and fibrillary. The amyloid rings had largely replaced the pericellular reticulum fibers. By combining the Laidlaw connective tissue and Congo red stains, it was noted that the remaining reticulum fibers usually lay between the myocardial cell membrane and the pericellular amyloid ring. No cellular reaction to the amyloid had occurred, and there was no acute myocardial necrosis or fibrosis. There was a greater degree of amyloid infiltration in the left ventricle as compared to the right. All the myocardial blood vessels, particularly the arteries, contained rounded, confluent amyloid deposits, which centered in the medial layer with extension into the adventitia (Fig. 4). A few atrophic nuclei of the smooth muscle cells remained. None of the cardiac vessels had significantly narrowed lumens. The interstitial, pericellular, and vascular amyloid distribution in each auricle was similar to that seen in the ventricles. In addition, there were extensive, rounded, irregular confluent amyloid masses in both the endocardial and pericardial layers. The auricular appendages contained organizing thrombi.

All the cardiac valves had a similar histologic appearance. The valvular endothelium was intact. Few connective tissue nuclei remained. The connective tissue fibers had lost their fibrillary character and had become swollen, eosinophilic, and amorphous. In all valves were small, irregularly rounded, centrally placed amyloid nodules.

Small amyloid deposits were noted in the media and the intima of the pulmonary artery. The media of almost all of the medium-sized pulmonary arteries and veins contained amyloid material. Less abundant deposits were present in the alveolar walls and in the submucosa of the bronchioles. The alveoli were atelectatic and many were lined by large, cuboidal epithelial cells. The alveolar walls showed a fibrous thickening in addition to that caused by the amyloid infiltration. Many macrophages and fewer red and white blood cells lay in the alveolar spaces.

There was moderate central sinusoidal congestion of the hepatic lobules, but the parenchymal cells were not altered. Large amyloid deposits were present in the fibrous septa of the cavernous hemangioma. Interstitial infiltration of all the layers of the gall bladder had occurred. The media of the arteries was similarly involved.

The Malpighian bodies and much of the splenic pulp had been replaced by amyloid material. Little was present in the walls of the central arteries. In the pulp, the material lay between the sinusoids, adjacent to the reticulo-endothelial cells lining the vascular channels.

There was no alteration of the pancreatic parenchyma. The media of some of the medium-sized arteries contained amyloid deposits.

An occasional renal glomerular tuft was distended with amyloid material. The convoluted tubules were dilated and many contained albumin and desquamated epithelial cells.

A diffuse amyloid infiltration of the connective tissue of the myometrium and endometrium was noted (Fig. 5). The amyloid material in the uterus was more pale and fibrillary than else-

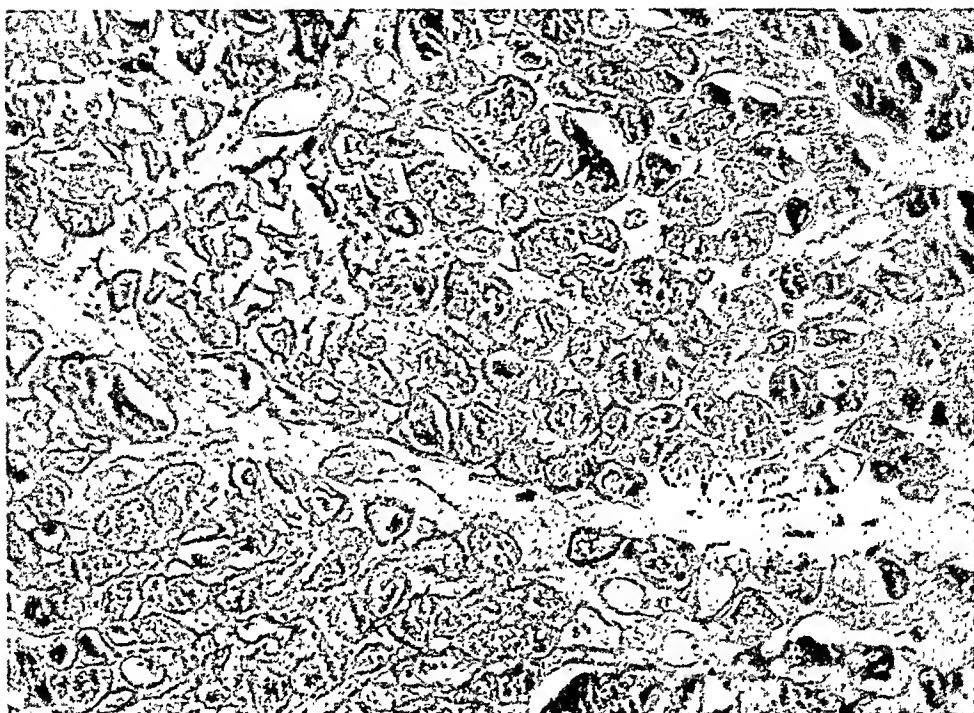


Fig. 3.—Myocardium showing pericellular amyloid rings, with atrophy or absence of muscle fibers, ($\times 120$). Crystal violet stain.

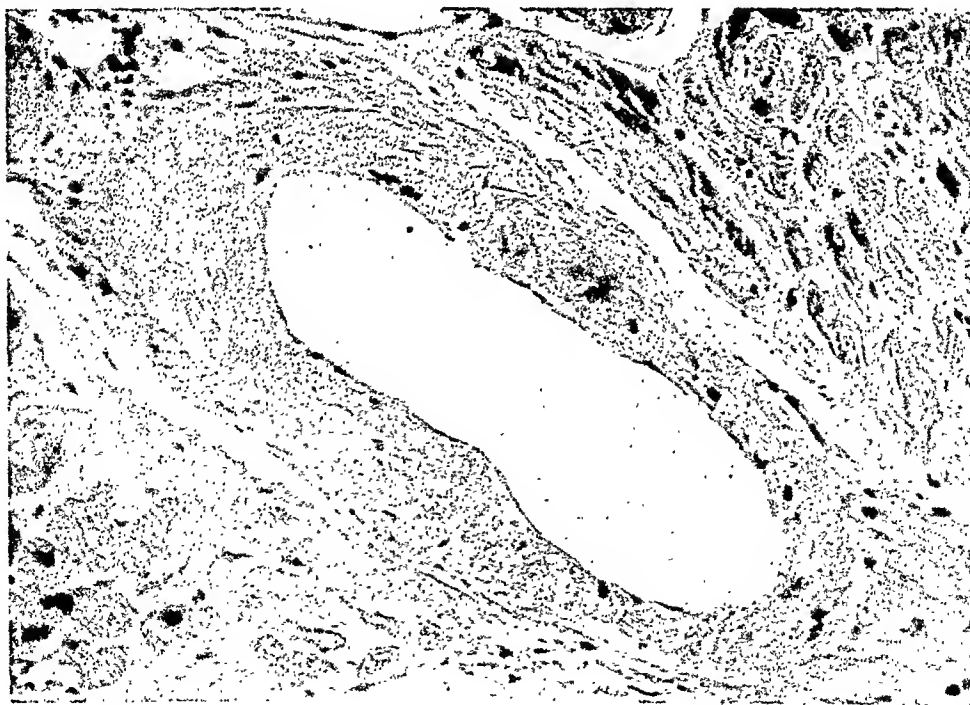


Fig. 4.—Myocardial vein with amyloid infiltration of its wall ($\times 250$). Hematoxylin and eosin stain.

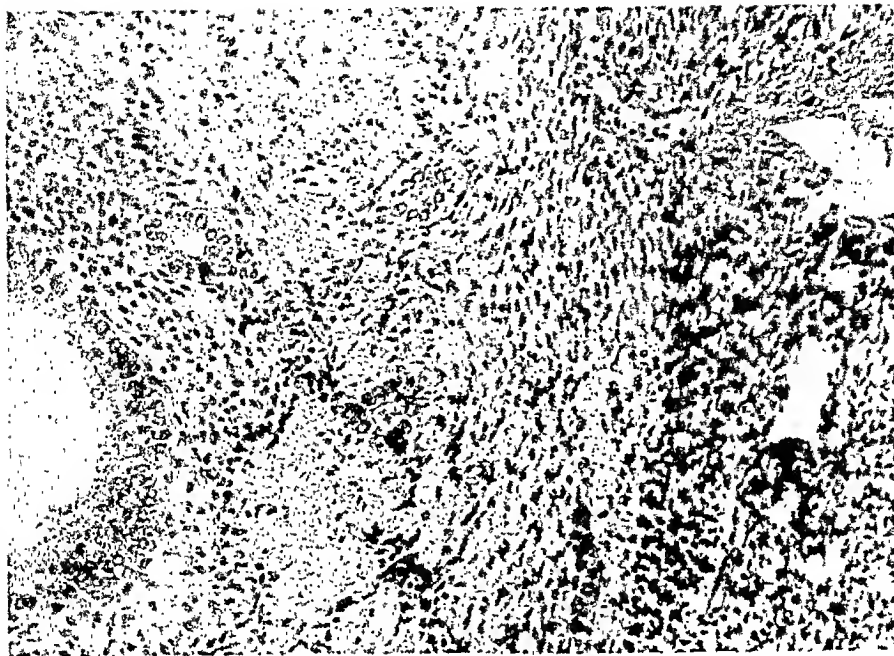


Fig. 5.—Endometrium showing interstitial amyloid infiltration ($\times 200$). Hematoxylin and eosin stain.

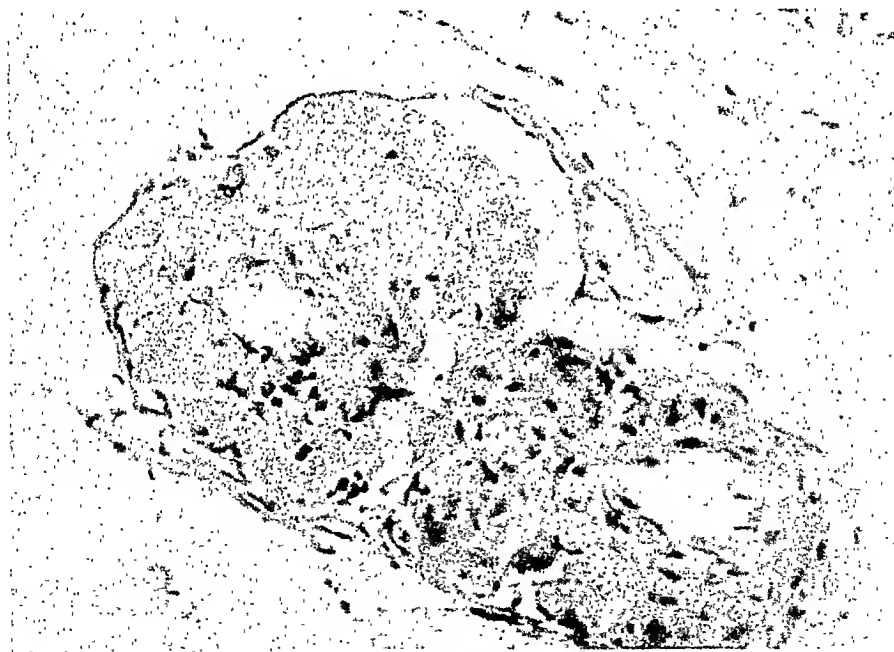


Fig. 6.—Small arteries of adrenal capsule showing extensive amyloid infiltration ($\times 250$). Hematoxylin and eosin stain.

where. The media of the small and medium-sized arteries in the uterine wall contained amyloid masses.

Similar interstitial and vascular masses of amyloid were present in the ovary and cervix. Minimal infiltration of the submucosa of the Fallopian tubes had occurred.

Amyloid deposition in the gastroenteric tract, including the esophagus, stomach, small bowel, and colon, had an unusual distribution. While the normal outlines of the muscular bundles remained, considerable atrophy or complete disappearance of many of the smooth muscle cells had occurred. This muscular alteration was due to compression by narrow fusiform or ovoid intercellular amyloid masses. Less abundant interstitial amyloid was present in the submucosa. Bulky deposits were encountered in both the arteries and veins of the gastroenteric tract.

Almost identical muscular, vascular, and submucosal deposits of amyloid were present in the urinary bladder.

The aortic intima was widened and was composed largely of hyalinized collagen. Small groups of lipid-containing macrophages were noted. Both the intimal and medial layers contained small interstitial amyloid deposits. There was interstitial amyloid infiltration of the media of the inferior vena cava. The bone marrow of the lumbar spine contained fat cells and hemopoietic tissue in normal proportions. Erythrocytic, myelocytic, and megakaryocytic elements were present in the usual numbers. Several small irregular amyloid deposits were noted. No plasma cells were identified.

The pituitary gland was not significantly altered. The acini of the thyroid gland were larger than normal and were distended with colloid substance. The cortical layer of the adrenal glands was moderately hyperplastic and the cortical cells were well supplied with lipid material. Minimal interstitial amyloid deposits were present in this layer. The medial layer of both the adrenal and periadrenal arteries and veins contained masses of amyloid substance (Fig. 6).

The left internal carotid artery had a thin wall. The intima and much of the media were the site of extensive atherosclerosis with calcification. The lumen contained a nonorganizing thrombus. The internal elastic membrane had been partially destroyed. Small amyloid deposits were noted in the media.

The lumens of both the right anterior and middle cerebral arteries were occluded by thrombi. That of the former had undergone early organization while the thrombus in the latter vessel was completely organized and recanalized. Amyloid was absent in these vessels.

The entire right frontal lobe was infarcted and consisted of a cystic space limited externally by the arachnoidal layer and posteriorly by a zone of gliosis. The cystic cavity contained a delicate vascular and glial network infiltrated with lipid-filled macrophages. There were no amyloid deposits in the central nervous system or in its blood vessels.

The amyloid material in all situations stained distinctly with the Congo red, crystal violet, and Mayer's stains but did not react with the iodine stain.

COMMENT

Amyloidosis is a disease in which a foreign protein, amyloid, is produced and deposited in certain tissues. Amyloid disease has been classified as follows: (1) secondary amyloidosis; (2) primary amyloidosis; (3) amyloidosis associated with multiple myeloma; (4) tumor-forming amyloidosis.³⁰ The most common form of amyloidosis is the secondary type which is ordinarily preceded by tuberculosis or chronic suppurative disease, though less often may follow a non-suppurative chronic inflammatory process. It has been shown that amyloid is composed of two protein fractions and one polysaccharide fraction.^{42,43} The vascular distribution of amyloid suggests that it may be deposited as a combination product, the result of a reaction between a fixed component of the vascular wall and some component of the serum globulin.³⁰ Hyperglobulinemia may occur with this reaction and the amyloid may represent tissue deposits of excess

globulin protein.⁴⁴ Hyperglobulinemia and amyloidosis may occur together in multiple myeloma. Of the cases of primary amyloidosis recorded in the literature, only five had absolute serum globulin levels over 2.2 per cent.^{17,21,34,35} It is probable that factors other than hyperglobulinemia are necessary for the development of amyloidosis.⁴⁵

While the relationship of amyloid deposition to abnormal protein metabolism in the secondary type of amyloidosis seems related to a bacterial antigen-antibody reaction, this sequence is less clear in the so-called primary form of the disease. Jaffé⁴⁷ has stressed the relationship between the allergic state acquired during a chronic infection and the appearance of amyloid substance, since secondary amyloidosis is most frequently found in tuberculosis where the occurrence of allergic reactions is so striking. Review of the histories in the published cases of primary amyloidosis reveals a number with possible etiologic agents, including past infections now quiescent,^{8,9,14,15,28} high protein diets,^{30,34} pyorrhea alveolaris,³⁴ and mycotic infections.³¹ In the case reported in this paper, food allergy was a possible etiologic agent. While hypersensitivity to foods or other ingested antigenic materials would suggest an etiologic basis for amyloid deposition due to an antigen-antibody relationship, Rowe⁴⁶ has seen no cases of amyloid disease in a large series of allergic patients. It has been noted⁴⁸ that a high protein diet may produce hyperglobulinemia.

Primary systemic amyloidosis is rare but is now a well-recognized entity. It differs from the more common secondary amyloidosis in several ways: (1) the absence of specific etiologic factors such as tuberculosis or chronic suppurative disease; (2) minimal or no deposition of amyloid in the liver, spleen, kidneys, and adrenal glands, the sites of maximum deposition in the secondary type of amyloid disease; (3) maximum deposition in the heart, lungs, skin, mucous membranes, striated muscles, and other tissues not usually involved in secondary amyloidosis; (4) formation of nodular amyloid tumors; (5) atypical reactions with specific amyloid stains.^{8,30}

There may be difficulty in the clinical diagnosis of this type of amyloidosis unless its fairly uniform signs and symptoms, characteristics, and distribution in tissue are kept in view. Overlapping of the characteristics of the four types of amyloid disease has been observed.

It is of interest to note that spontaneous amyloidosis in mice resembles primary amyloidosis of human beings in its distribution, while the amyloidosis produced in these animals by injections of sodium caseinate bears a resemblance to the secondary form of the disease as seen in the human being.⁵²

To date, forty-four cases of primary systemic amyloidosis have been recorded in the literature;¹⁻³⁷ forty of these have been summarized by Koletsky and Stecher³⁰ and by Lindsay and Knorp.³⁶ Additional cases have since been reported by Brown and Selzer³⁵ and Golden.³⁷ Cases recorded by Pick¹² and by Bannick and co-workers²⁰ had been overlooked. Other papers dealing with systemic and atypical amyloidosis, with cardiac involvement, have been listed⁴⁹⁻⁵¹ in the *Cumulative Index Medicus* but due to war conditions are not available for study. With the present recorded case, a total of forty-five cases with forty-three

autopsy reports are available for review. Two patients were alive at the time the reports were made.

Of the forty-five cases, twenty-three showed clinical evidence of cardiac failure during the course of the illness. In eighteen of the forty-three fatal cases, it was stated that cardiac failure was the immediate cause of death. In one case with extensive valvular deposits of amyloid, death due to cardiac failure was the result of coronary atherosclerosis and myocardial infarction, though undoubtedly the valvular amyloid contributed to cardiac failure before death.³⁶ From the clinical and pathologic evidence available in the published cases, this author felt that in fourteen patients death from myocardial failure was the result of cardiac amyloid infiltration. In two additional instances, this possibility was likely, though not definite. Of the forty-three fatal cases in which autopsies were done, thirty-nine showed some degree of amyloid deposition in the heart. In a few cases, the amyloid deposition was limited to small cardiac blood vessels.^{33,35}

Clinical evidence of cardiac failure due to amyloid deposition in the heart may be difficult to evaluate. Signs and symptoms suggesting cardiac disease may be produced by amyloid involvement (1) of the lungs, with chronic cor pulmonale, (2) of the trachea, or (3) of the mediastinum, or by the anemia which often is present.³⁰ Coronary atherosclerosis or hypertension may be complicating factors in the cardiac failure occurring in primary amyloid disease.^{32,36}

Amyloidosis may produce cardiac failure in several ways: (1) deposition in the pulmonary vessels and alveolar walls with resulting chronic cor pulmonale; (2) deposition in the cardiac blood vessels, including arteries, veins, and capillaries; (3) diffuse or localized nodular interstitial amyloid infiltration with or without secondary degeneration of the myocardial fibers; (4) pericardial or endocardial deposits; (5) extensive valvular deposits producing stenosis or insufficiency; (6) often a combination of several sites of deposition.

Review of the symptoms in many of the recorded cases of primary systemic amyloidosis are those of cardiac insufficiency and insufficient blood flow to the myocardium. These include dyspnea, cyanosis, weakness, precordial pain, paroxysmal dyspnea, orthopnea, palpitation, and cough. Physical examination has revealed edema, hydrothorax, ascites, cardiac enlargement, cardiac murmurs, tachycardia, auricular fibrillation, venous engorgement and pulsation, gallop rhythm, tick-tack sounds, and pulsus alternans.

The widespread systemic distribution of amyloid substance, with resulting signs and symptoms, usually presents a bizarre, though somewhat uniform, clinical picture. The sites of involvement and the systemic signs and symptoms in the majority of cases have already been tabulated,^{30,36} these may point to an amyloid background for the cardiac manifestations.

Lesions of the skin are fairly common. These have been described as opalescent and papular,³¹ opalescent, firm, and nodular,¹⁵ sclerodermic,^{8,14,22} papular plus plaquelike scleroderma,¹³ weeping eczematous,³⁶ and pink striae beneath the nails of the fingers and toes.³⁶ These deposits in the skin are, of course, accessible for diagnostic biopsies. In the majority of cases where there was an antemortem diagnosis, it was made by this method from sites including the

skin,^{6,13,25} buccal mucosa,²¹ skeletal muscles,^{13,27} vagina,²⁵ and stomach.³⁷ In at least one instance³⁶ amyloid in the tissues removed was not recognized. It has been pointed out³⁰ that, because of the variability of the staining reactions in primary amyloidosis, tissue suspected of containing amyloid should be stained with several of the known amyloid stains (Congo red, crystal violet, and iodine and sulfuric acid).

Amyloid infiltration of the gastroenteric tract has been a frequent finding in this group of cases and has led to the following symptoms and signs: diarrhea, constipation, abdominal pain, nausea, vomiting, distention, intestinal hemorrhage, intestinal obstruction, epigastric tenderness, hematemesis, anorexia, and postprandial pyrosis. In three cases^{8,36,37} gastric ulceration had occurred.

Enlargement of lymph nodes may be localized or generalized and may result in a localized amyloid tumor.³⁶

Enlargement of the tongue has been a frequent finding, often has suggested neoplastic disease, and has been accompanied by dysphonia and dysphagia. The buccal and nasal mucosa, the larynx, and the trachea have been sites of infiltration. Nasal hemorrhage³⁶ and laryngeal obstruction⁹ have been described. Facial rigidity has resulted from infiltration of the skin, subcutaneous tissues, and muscles.¹⁵ Extensive involvement of skeletal muscle has produced the picture of myotonia with an unusual degree of progressive fatigue and weakness. Deposits in posterior roots, sympathetic ganglia, and peripheral nerves have resulted in muscular weakness.²⁸ Central nervous system involvement has not been described.

Arthritis may be simulated, and involvement of bones, joints, and tendons has led to limitation of motion, disturbances in gait, and pathologic fractures.³⁰ Collapse²³ or narrowing³⁶ of vertebral bodies as the result of amyloid infiltration has occurred. Purpura is a common symptom and is presumably due to amyloidosis of the blood vessels,³⁰ though anemia and leucopenia resulting from amyloidosis of the marrow³⁶ suggests a thrombocytopenic basis for the bleeding tendency.

In many cases involvement of small blood vessels, especially arterial, has been widespread. Deposition in all portions of the genitourinary tract in both men and women has been reported.

In addition to biopsy of accessible amyloid lesions, the intravenous Congo red test may be helpful in establishing the diagnosis of amyloidosis. Bennhold's Congo red test⁶¹ has recently been evaluated by Stemmerman and Auerbach⁶² in a large group of patients with secondary amyloidosis. These authors considered a 90 to 100 per cent absorption of dye as a positive test. Where only minimal amounts of amyloid were present, false negative tests were likely to result. False positive results occurred with technical errors and in the presence of renal tubular damage. The Congo red test has been done in ten patients with primary amyloidosis. In five of these,^{13,21,23,34,35} the results were considered positive with the percentage of intravenously administered Congo red absorbed from the blood at one hour ranging from 60 to 100 per cent. In the five in whom the test was considered negative,^{17,25,27,30,37} the percentage of dye absorbed by the tissues

at one hour ranged from 0 to 35 per cent. In this small group of cases, there was no apparent correlation between the amount of amyloid found at autopsy (or estimated clinically) and the amount of Congo red removed from the blood. This test was not done in any of those patients in whom amyloidosis of the heart was the cause of death.

In amyloidosis secondary to tuberculosis or chronic suppuration, the heart is rarely involved, while the maximum deposition usually occurs in the spleen, liver, kidneys, and adrenal glands. In fifty-seven tuberculous patients observed post mortem, amyloid deposits in the heart were not encountered.⁵³ Amyloidosis is less common in chronic nonsuppurative disease,⁵⁴ although in severe rheumatoid arthritis amyloidosis has been reported in a few instances.⁵⁵ In experimental amyloidosis produced by injection of sodium caseinate, amyloidosis of the heart was observed. There were perivascular deposits in the myocardium and in the leaflets at the valves, particularly the mitral.⁴⁷

Primary amyloidosis is generally characterized by an atypical amyloid distribution, often with cardiac involvement.³⁰ In the forty-three available autopsy reports, cardiac amyloidosis was encountered in thirty-nine instances. In one case³⁴ the amyloid distribution was similar to that seen in the secondary type of the disease. Conversely, several reports of secondary amyloidosis with the distribution characteristic of the primary type are available. In Kann's case⁵⁶ in which the amyloidosis presumably was secondary to syphilis, there was extensive substitution of the myocardium by amyloid substance. Both the auricular and ventricular walls were involved and there were nodular deposits in the endocardium. Small amounts of amyloid were present in the cardiac valves. Virchow⁵⁷ apparently was the first to observe amyloid deposition in the heart. Not until 1907 was the cardiac distribution adequately described. In eight patients with secondary amyloidosis, von Huebschmann⁵⁸ found amyloid in the connective tissues and blood vessels of the myocardium but rarely in the valves or endocardium. None of the eight patients had cardiac manifestations.

More recently, other cases of cardiac amyloid, secondary to chronic suppurative disease, have been reported. In Budd's case⁵⁹ in which a prostatic adenocarcinoma and urinary suppuration caused death, amyloid was encountered in the small coronary blood vessels, myocardium, and endocardium. Only minimal amounts of amyloid were present in the pulmonary and mitral valves.

In the case recorded by Spain and Barrett,⁶⁰ amyloidosis secondary to suppurative bronchiectasis was accompanied by amyloid deposits in the heart which had produced clinical evidence of cardiac failure, including dyspnea, cyanosis, edema of the legs, pleural effusion, and an increase in circulation time. The electrocardiogram showed left-axis deviation and low voltage in all leads.

The visceral pericardium has often been one site of cardiac amyloid deposition in primary systemic amyloidosis. Nodular amyloid strata on this layer have been described.¹ Both small and large discrete amyloid nodules often are present. In one case⁸ both pericardial layers were firm and thickened. Gerstel¹⁴ described a grayish-gold, jellylike membrane on the surface of the heart. The pericardial amyloid may take the form of small flecks¹⁵ or pearly-gray 1 mm.

nodules.³⁰ In one case¹⁹ there were deep parallel grayish-yellow furrows in the right auricular epicardium. At times the epicardium is thickened and grayish yellow in color.²² In Kerwin's first case, both pericardial layers were studded with firm, translucent grayish 1 mm. nodules.²⁶ The nodules were larger but fewer in Golden's case.³⁷ In the pericardial layer, the amyloid has had both a vascular and an interstitial distribution. The latter has included amyloid rings about the pericardial fat cells in several of the recorded cases^{1,4,18} and in the case reported in this paper. These pericellular amyloid deposits have also been seen in the periadrenal fat.³² Peters⁶⁶ has pointed out that pericellular amyloid deposition may occur in many situations and has suggested that the deposition of amyloid on cell surfaces may be the initial process in amyloidosis. From the published reports, it seems unlikely that amyloid in the pericardial layers has contributed significantly to the production of cardiac failure.

The bulk of the cardiac amyloid has had a myocardial distribution in many of the cases and is most important in the mechanism of cardiac failure. Both the auricular and ventricular walls may be hypertrophied and thickened. When the myocardial amyloid is diffusely distributed, these walls have been described as hard or firm, pale, grayish tan or golden brown, waxy or translucent, homogeneous or glassy. The auricular walls are often stiff and leathery. The involved myocardium tends to be rigid and resistant to cutting, and the chambers retain their globular shape rather than collapsing. The diffuse myocardial amyloid deposits may appear as irregular, translucent, pearly-gray or yellowish-opaque streaks, gleaming flecks, or trabeculae or may be more localized as large or small nodular masses, often projecting above the cut surface. One to 3 cm. amyloid nodules have been noted in the ventricular walls.^{10,15}

Microscopic examination of the myocardium in many cases has disclosed a rather consistent pattern of distribution of the amyloid substance. The myocardial blood vessels often contained mural amyloid deposits lying in any or all of their layers. In a few instances, these have appeared in the main coronary arteries. In one case, subendothelial amyloid at least contributed to narrowing of the lumens of the main coronary arteries.³⁶ More often, the medium-sized and small coronary arteries were involved with distinct narrowing of the vessel lumens. The veins, arterioles, and capillaries have also been the site of amyloid infiltration. The marked degree of vascular narrowing associated with this infiltration and the resulting diminution of blood flow to the myocardium has undoubtedly been a significant factor in failure of the myocardium in many of the cases.

Even more important in the mechanism of cardiac failure has been the diffuse interstitial amyloid infiltration of the myocardium. Aside from the deleterious effects on the muscle cells, the extensive amyloid network must have interfered greatly with the normal range of contraction and relaxation of the cardiac chambers. In twenty of the cases it has been noted that narrow bands of amyloid substance had been deposited about individual myocardial fibers appearing on cross section as imprisoning rings or sheaths. At times, one portion of this amyloid sheath may invaginate into the cytoplasm of the cell. The myocardial

fibers may be compressed, narrowed, or displaced and frequently have been severely damaged. They were often atrophic, vacuolated, fragmented, necrotic, or contained lipid or pigment deposits. Nuclear degeneration was common. With excessive deposition, the muscle cells disappeared, leaving empty amyloid rings or almost solid amyloid sheets. The fibers in those areas with less or no amyloid often compensated by hypertrophy.

Beneke and Bönning⁴ were of the opinion that the amyloid material was primarily deposited on and about the muscle cells. In the light of the observations of Peters,⁶⁶ this may be true. Larsen,¹¹ however, pointed out that the intercellular and pericapillary deposits were continuous and felt that the pericellular amyloid originated in the blood vessels. This same continuity has been noted by others^{32,37} and was seen in the case reported in this paper. The intercellular amyloid appeared to extend from extensive arterial and arteriolar deposits in one instance.³⁷

Koller¹⁶ described the pericellular amyloid as being deposited in the perimysium of the myocardial fibers. By combining the Congo red and a silver reticulum stain on the same section, it was possible in the case reported in this paper to demonstrate that the amyloid had largely replaced the pericellular reticulum and, furthermore, that when the reticulum persisted, it lay between the cell membrane and the pericellular amyloid ring.

Where the amyloid deposits were fewer and more localized, the material lay in rounded, confluent, nodular masses, showing neither a distinct cellular nor vascular origin.

In the majority of recorded cases, amyloid was present in the endocardial layer, often as stratified or nodular deposits and occasionally continuous with the myocardial amyloid. In one case³⁶ where both valvular and mural endocardial amyloid was particularly abundant, this material lay immediately beneath the endothelium. In many instances, the amyloid infiltrates mainly the deep endocardial layers.

Of the forty-five cases of primary systemic amyloidosis, sixteen had amyloid deposits in the cardiac valves. Valvular involvement is often slight and only microscopically demonstrable. In a smaller number of cases, the valvular deposition was more striking. Discrete amyloid nodules, with thickening and rigidity of several of the valves, have been described.¹ Grayish-white 1-3 mm. discrete nodules may be limited to the mitral valve.⁷ In Koller's case¹⁶ both the mitral and tricuspid valves were hard, thickened, and stenotic. The valvular amyloid in one instance appeared as grayish-red warty nodules on all valves except the aortic.¹⁹ Fine shotty amyloid nodules were present along the free margins and auricular surfaces of the mitral and tricuspid valves in the first case recorded by Kerwin.²⁶ In another case²⁹ there was a plaquelike thickening of the line of closure of the mitral valve. Amyloid nodules may lie both in the cusp and the annulus fibrosis of the cardiac valves.³⁷ In two of the recorded cases^{30,36} there were unusually abundant amyloid masses in the cardiac valves. In Koletsky and Stecher's case³⁰ all four valves showed nodular deposits of amyloid, particularly in the aortic and mitral valves. These nodules had so involved the base and free

margins of the leaflets as to produce thickening, rigidity, immobility, and stenosis. These authors explained the extensive involvement of the leaflets as a direct extension of amyloid from the ring of the valve. All four valves were also extensively infiltrated with amyloid in the case recorded by Lindsay and Knorp.³⁶ In this instance, the valvular surfaces, particularly of the pulmonary and tricuspid valves, were covered by smooth, nodular, glistening, translucent, yellowish-white, soft amyloid substance, which had led to a distinct decreased mobility of the cusps. The chordae tendineae were similarly covered, but their fibrous structure was visible through the amyloid coating. In this case, the origin of the amyloid from the adjacent endothelium was apparent. In both of these cases^{30,36} it was considered probable that the valvular amyloid infiltration played a significant role in the mechanism of cardiac failure.

In addition to direct cardiac infiltration by amyloid material, cardiac failure may also result from pulmonary amyloid disease. Chronic cor pulmonale with right ventricular hypertrophy and dilatation on a pulmonary amyloid basis has been recorded on several occasions^{11,32,33} and also was noted in the case reported in this paper. The pulmonary amyloid infiltration in the case reported by Sappington and co-workers³³ was extreme. There was universal involvement of both the arteries and veins plus almost complete amyloid infiltration of the alveolar walls. Presumably the latter was related to capillary infiltration. There was a marked reduction in the diameter of the lumens of the involved vessels, which by interference with pulmonary blood flow had produced right ventricular hypertrophy. A roentgenogram of the chest showed enlargement of the cardiovascular silhouette and an indefinite haziness of the lung fields. In one case¹¹ some of the amyloid masses in the alveolar walls were so abundant as to cause bulging of the alveolar epithelium into the acinar space. In the patient described in this paper, there was also abundant pulmonary vascular and interstitial amyloid which produced right ventricular hypertrophy and undoubtedly contributed in part to the cardiac failure. Pearson and co-workers³² were of the opinion that the obliterating pulmonary vascular amyloid infiltration in one of their cases was a factor in the production of right ventricular failure.

Hypertension has been present in four of the recorded cases.^{23,28,32,37} In the first, hypertension was due to renal amyloidosis. In the second, gross renal scarring and microscopic amyloid were present, but whether the two were related to each other and to the elevated blood pressure was not stated. In the last two cases, renal amyloid was not present, and presumably the hypertension was coincidental and essential in type. In one case³² the authors felt that cardiac failure was the result, in part, of hypertension.

Electrocardiographic studies were done on twelve of the forty-five recorded cases.^{11,26-29,31-34,36} In nine of the twelve cases, myocardial amyloid infiltration was considered to have been the cause of death. In six of these, low voltage in the electrocardiographic record was a prominent feature. Katz⁶³ has pointed out that one cause of low voltage in the QRS complex is a diffuse myocardial alteration which prevents a normal flow of current through the ventricular tissues. The myocardial amyloid in this group of patients appears to have produced a

distinct conduction disturbance in the ventricular walls. In one case³⁴ the P-R interval was slightly prolonged. Alteration of the P wave was not noted in any of the cases. Auricular fibrillation was present in one case,¹¹ and ventricular premature contractions were noted in two cases. Axis deviation was more often to the left than to the right. In one case with an abnormal electrocardiogram, the responsible myocardial lesion was due to arteriosclerosis and not amyloid.³⁶

Treatment of primary systemic amyloidosis to date has been symptomatic, expectant, and directed toward the complications. In only twelve cases has an ante-mortem diagnosis been made, usually by biopsy. The rate of progress of the disease is variable. Duration of life from the onset of symptoms has varied from four months¹⁶ to fourteen years³⁰ and sixteen years.³⁷

It is well known that recovery from secondary amyloidosis may occur, usually following retrogression of the responsible inflammatory process. Trasoff and co-workers⁵⁵ have cited some twenty-nine instances of recovery recorded since 1880. Experimental amyloidosis in mice produced by protein administration has receded when such treatment was terminated.^{64,65} Reabsorption of experimentally produced splenic amyloid appeared to be the result of leucocytic and capillary invasion, amyloid fragmentation, and foreign body giant cell activity.⁴⁵ Grayzel and co-workers⁶⁵ found that administration of liver substance either resulted in absorption or delay in deposition of experimentally induced amyloid in mice. These studies have led to successful therapy of secondary human amyloidosis.⁴¹ Despite the continuation of the underlying process, thirteen children with chronic suppurative disease were treated orally with powdered whole liver extract. With the exception of four dying with advanced tuberculosis, this group showed marked improvement or complete recovery from amyloid disease. Early signs of recovery were diminution in size of the liver and spleen, with the other signs and symptoms regressing more slowly. It was emphasized that the recovery rate was not regularly progressive, suggesting a variable chemical composition of the amyloid substance.

More recently Jacobi and Grayzel⁶⁷ recorded the effects of the oral administration of 4 to 8 Gm. of desiccated powdered whole liver preparation to patients with amyloidosis secondary to tuberculosis. Treatment was continued for a year or more, and of sixteen patients, nine were cured as demonstrated by the disappearance of symptoms and the absence of Congo red retention.

While there are undoubtedly certain differences in the composition of amyloid in the primary and secondary forms of the disease, therapy with liver substance may be found to be of benefit in the primary type.

Clinical and laboratory recognition of primary amyloidosis, further elucidation of the responsible mechanisms at work, with their subsequent removal or amelioration, may result in recovery as in experimental and secondary amyloidosis. Accumulating evidence suggests that the fundamental disturbance is identical in all types of amyloid disease and that when the basic mechanism is known, primary amyloidosis will be classified as a "secondary" type.

SUMMARY

1. A case of primary systemic amyloidosis is reported. The duration of the illness was one year. Death was due to cardiac failure, the result of extensive amyloid infiltration of the myocardium.

2. There are now forty-five cases of primary systemic amyloidosis recorded in the literature. These have been reviewed, and their cardiac manifestations and involvement by amyloid substance have been summarized and discussed.

REFERENCES

1. Wild, C.: Beitrag zur Kenntnis der amyloiden und hyalinen Degeneration des Bindegewebes, *Beitr. z. path. Anat. u. z. allg. Path.* **1**: 177, 1886.
2. Steinhaus, F.: Ueber eine seltene Form von Amyloid- und Hyalin-Infiltration am Circulations- und Digestionsapparat, *Ztschr. f. klin. Med.* **45**: 375, 1902.
3. Ritter, E.: Ein Fall von ausgedehnter Hyalinbildung in Arterien, *Virchows Arch. f. path. Anat.* **192**: 536, 1908.
4. Beneke, R., and Bönning, F.: Ein Fall von lokaler Amyloidose des Herzens, *Beitr. z. path. Anat. u. z. allg. Path.* **44**: 362, 1908.
5. Beneke, R.: Ueber lokale Amyloidose des Herzens, *Centralbl. f. allg. Path. u. path. Anat.* **33**: 240, 1922.
6. Königstein, H.: Ueber Amyloidose der Haut, *Arch. f. Dermat. u. Syph.* **148**: 330, 1925.
7. Silwer, H., and Lindblom, A. F.: Ein Fall von allgemeiner Amyloidose ohne nachweisbare Ursache (Sogen. idiopathische Amyloidose), *Acta. med. Scandinav.* **64**: 529, 1926.
8. Lubarsch, O.: Zur Kenntnis ungewöhnlicher Amyloidablagerungen, *Virchows Arch. f. path. Anat.* **271**: 867, 1929.
9. Picchini, L., and Fabris, A.: Sulle paramiloidosi, *Arch. per le sc. med.* **54**: 551, 1930.
10. Warren, S.: Amyloidosis of the Muscular Systems, *Am. J. Path.* **6**: 161, 1930.
11. Larsen, R. M.: A Pathological Study of Primary Myocardial Amyloidosis, *Am. J. Path.* **6**: 147, 1930.
12. Pick, L.: Ueber atypische Amyloidablagerung, *Klin. Wchnschr.* **10**: 1515, 1931.
13. Gottron, H.: Systematisierte Haut-Muskel-Amyloidose unter dem Bilde eines Skleroderma amyloidosum, *Arch. f. Dermat. u. Syph.* **166**: 584, 1932.
14. Gerstel, G.: Ueber atypische Lokalisation des Amyloids, insbesondere über die Makroglossia amyloides diffusa, *Virchows Arch. f. path. Anat.* **283**: 466, 1932.
15. Mollow W., and Lebell: Zur Klinik der systematisierten Amyloidablagerung, *Wien. Arch. f. inn. Med.* **22**: 205, 1932.
16. Koller, F.: Ueber atypische Amyloidose als Ursache von Herzinsuffizienz, *Schweiz. med. Wchnschr.* **13**: 522, 1932.
17. von Bonsdorff, B.: Atypisk Amyloidosis, *Finska läk.-sällsk. handl.* **75**: 447, 1933.
18. Straus, A.: Ueber Paramyloidose, *Virchows Arch. f. path. Anat.* **291**: 219, 1933.
19. Israel, I.: Ein Fall von "lokalem Amyloid," *Med. Dissert., Tübingen*, 1933, Bochum-Langendreer.
20. Bannick E. G., Berkman, J. M., and Beaver, D. C.: Diffuse Amyloidosis. Three Unusual Cases. A Clinical and Pathological Study, *Arch. Int. Med.* **51**: 978, 1933.
21. Michelson, H. E., and Lynch, F. W.: Systematized Amyloidosis of the Skin and Muscles, *Arch. Dermat. & Syph.* **39**: 805, 1934.
22. Gaupp, A.: Ein Fall von generalisierter, atypischer Amyloidose (Paramyloidose), *Med. Dissert., Munich*, 1934.
23. Gerber, I. E.: Amyloidosis of the Bone Marrow, *Arch. Path.* **17**: 620, 1934.
24. Perla, D., and Gross, H.: Atypical Amyloid Disease, *Am. J. Path.* **11**: 93, 1935.
25. Reimann, H. A., Koucky, R. F., and Eklund, C. M.: Primary Amyloidosis Limited to Tissues of Mesodermal Origin, *Am. J. Path.* **11**: 977, 1935.
26. Kerwin, A. J.: Idiopathic Amyloid Disease of the Heart, *J. Lab. & Clin. Med.* **22**: 255, 1936.
27. Weber, F. P., Cade, S., Stott, A. W., and Pulvertaft, R. J. V.: Systematized Atypical Amyloidosis With Macroglossia, *Quart. J. Med.* **6**: 181, 1937.
28. De Navaquez, S., and Treble, H. A.: A Case of Primary Generalized Amyloid Disease With Involvement of Nerves, *Brain* **61**: 116, 1938.
29. Haenisch, R.: Ein Fall von Paramyloidose, *Frankfurt. Ztschr. f. Path.* **52**: 107, 1938.
30. Koletsky, S., and Stecher, R. M.: Primary Systemic Amyloidosis—Involvement of Cardiac Valves, Joints and Bones, With Pathologic Fracture of the Femur, *Arch. Path.* **27**: 267, 1939.

31. Binford, C. A.: Primary Amyloid Disease, *Arch. Path.* **29**: 314, 1940.
32. Pearson, B., Rice, M. M., and Dickens, K. LaV.: Primary Systemic Amyloidosis—Report of Two Cases in Negroes With Special Reference to Certain Histological Criteria for Diagnosis, *Arch. Path.* **32**: 1, 1941.
33. Sappington, S. W., Davie, J. H., and Horneff, J. A.: Primary Amyloidosis of the Lungs, *J. Lab. & Clin. Med.* **27**: 882, 1942.
34. Dillon, J. A., and Evans, L. R.: Primary Systemic Amyloidosis, *Ann. Int. Med.* **17**: 722, 1942.
35. Brown, H. A., (Capetown, South Africa), and Selzer, G.: A Case of Primary Amyloidosis, *Clin. Proc.* **3**: 227, 1944.
36. Lindsay, S., and Knorp, W. F.: Primary Systemic Amyloidosis, *Arch. Path.* **39**: 315, 1945.
37. Golden A.: Primary Systemic Amyloidosis of the Alimentary Tract, *Arch. Int. Med.* **75**: 413, 1945.
38. Weiss, S.: Disease of the Heart and Aorta Which Are not Well Recognized, *M. Clin. North America*, **23**: 1323, 1939.
39. Saphir, Otto: Isolated Myocarditis, *AM. HEART J.* **24**: 167, 1942.
40. Weiss, S., Stead, E. A., Jr., Warren, J. V., and Bailey, O. T.: Schleroderma Heart Disease, *Arch. Int. Med.* **71**: 749, 1943.
41. Grayzel, H. G., and Jacobi, M.: Secondary Amyloidosis: Results of Therapy With Desiccated Whole Liver Powder, *Ann. Int. Med.* **12**: 39, 1938.
42. Hass, G., and Schultz, B. Z.: Amyloid I—Methods of Isolating Amyloid From Other Tissue Elements, *Arch. Path.* **30**: 240, 1940.
43. Hass, G.: Amyloid II—The Isolation of a Polysaccharide From Amyloid-Bearing Tissues, *Arch. Path.* **34**: 92, 1942.
44. Riemann, H. A., and Eklund, C. M.: Long-Continued Vaccine Therapy As a Cause of Amyloidosis, *Am. J. M. Sc.* **190**: 188, 1935.
45. Dick, G. F., and Leiter, L.: Some Factors in the Development, Localization, and Reabsorption in Experimental Amyloidosis in the Rabbit, *Am. J. Path.* **17**: 741, 1941.
46. Rowe, A. H.: Personal communication.
47. Jaffé, R. H.: Amyloidosis Produced by Injections of Proteins, *Arch. Path.* **1**: 25, 1926.
48. Rowe, A. H.: The Effect of Muscular Work, Diet, and Hemolysis on the Serum Protein, *Arch. Int. Med.* **19**: 499, 1917.
49. Saisalo, P., and Ritaman, V.: Atypical Amyloidosis With Special Consideration of Heart, *Acta. Med. Scandinav.* **116**: 260, 1944.
50. Halbfleisch, H. H.: Amyloidosis of Heart, *Frankfurt. Ztschr. f. Path.* **54**: 319, 1940.
51. Rodriguez, M., and Valente, P.: Atypical Generalized Amyloidosis, *Rev. clin. españ.* **10**: 310, 1943.
52. Dunn, T. B.: Relationship of Amyloid Infiltration and Renal Disease in Mice, *J. Nat. Cancer Inst.* **5**: 17, 1944.
53. Altnow, H. O., Van Winkle, C. C., and Cohen, S. S.: Renal Amyloidosis—A Further Study of the Clinical Course and Pathologic Lesions in Fifty-Seven Cases, *Arch. Int. Med.* **63**: 249, 1939.
54. Moschowitz, E.: Clinical Aspects of Amyloidosis, *Ann. Int. Med.* **10**: 73, 1936.
55. Trasoff, A., Schneeberg, N., and Scarf, M.: Recovery From Rheumatoid Arthritis Complicated by Amyloidosis in a Child, *Arch. Int. Med.* **74**: 4, 1944.
56. Kann, G.: Ein von isolierter Amyloidose des Herzens. *Virchows Arch. f. path. Anat.* **237**: 22, 1922.
57. Virchow, R.: Cellular Pathology, American edition, New York, 1858, Robert M. Dewitt, p. 411.
58. Huebschmann, P.: Ueber Herzamyloid, *Virchows Arch. f. path. Anat.* **187**: 35, 1907.
59. Budd, J. W.: Primary Amyloid Disease of the Heart, *Am. J. Path.* **10**: 299, 1934.
60. Spain, D. M., and Barrett, R. C.: Amyloidosis in Atypical Sites (Cardiac Valves and Larynx), *Arch. Path.* **38**: 203, 1944.
61. Bennhold, H.: Ueber die Ausscheidung intravenos einverleibten Kongorotes bei den verschiedensten Erkrankungen insbesondere bei Amyloidosis, *Deutsches Arch. f. klin. Med.* **143**: 32, 1923.
62. Stemmerman, M. G., and Auerbach, O.: The Value and Limitations of the Congo red Test for Amyloidosis, *Am. J. M. Sc.* **208**: 305, 1944.
63. Katz, L. N.: Electrocardiography, Philadelphia, 1941, Lea & Febiger.
64. Morgenstern, Z.: Zur Frage über Amyloidose und Resorption, *Virchows Arch. f. path. Anat.* **259**: 698, 1926.
65. Grayzel, H. G., Jacobi, M., Warshall, H. B., Bogin, M., and Bolker, H.: Amyloidosis—Experimental Studies, *Arch. Path.* **17**: 50, 1934.
66. Peters, J. T.: Epicellular and Pericellular Depositions of Amyloid as the Starting Point of Amyloidosis, *Arch. Path.* **35**: 832, 1943.
67. Jacobi, M., and Grayzel, H.: Generalized Secondary Amyloidosis. *J. Mt. Sinai Hosp.* **12**: 339, 1945.

SOME OBSERVATIONS ON THE PATHOGENESIS OF EDEMA IN CARDIAC FAILURE

FRANCIS REICHSMAN, M.D., AND HAROLD GRANT, M.D.

DALLAS, TEXAS

THE pathogenesis of cardiac edema has been the subject of extensive investigation and many explanations have been given. The classical work of Starling¹² cleared up much of the confusion which had existed in the theories of the pathogenesis of all forms of edema. At present the most widely accepted explanation is that cardiac edema is due to an increase in the filtration of water and electrolytes through the capillaries into the extracellular space secondary to a rise in the hydrostatic pressure within the capillaries and elevated venous pressure. The rise in venous pressure is caused by failure of the right heart. The absence of edema in left heart failure and in peripheral circulatory failure is good evidence that circulatory retardation is not an important factor.²

Krogh, Landis, and Turner⁹ have shown that in experimental venous congestion the rate of edema formation is increased as the colloidal osmotic pressure is decreased. Many patients with congestive heart failure have slightly decreased plasma proteins, though the levels reached are very rarely low enough to explain in itself the formation of edema.^{10,11,14} Warren and Stead¹⁵ and Bramkamp¹ have shown that cardiac edema fluid does not contain an increased amount of protein. This is good evidence that increased capillary permeability is not a significant factor.

In patients with congestive heart failure the urinary output is low and no satisfactory explanation of this has yet been given. Several observers^{3,6} have demonstrated that there is an increased blood volume and hemodilution in congestive heart failure rather than the lowered blood volume and hemoconcentration which would be expected if the oliguria were a manifestation of the increased transudation of water into the extracellular space. Fremont-Smith⁴ showed that following the ingestion of water, normal subjects had less hemodilution and more diuresis than patients with cardiac edema. Thus one has to assume that there is also a renal factor in cardiac edema. Fitcher and Schroeder⁵ further confirmed this idea by demonstrating impairment in the ability of the kidneys to excrete injected sodium chloride in four patients convalescing from severe congestive heart failure.

From the Department of Medicine of the Southwestern Medical College and the Parkland Hospital.

Aided by grants from the John and Mary Markle Foundation and from the DAZIAN Foundation.
Received for publication March 1, 1946

In 1944 a paper was published which aroused much comment and interest and in no small part gave rise to the study which is reported here. Warren and Stead¹⁵ gave excess sodium chloride to two patients just after they had become compensated following a bout of severe congestive heart failure. They reported that both of the subjects showed a significant weight gain before the venous pressure rose. As a result of this experiment they offered the following explanation of the mechanism of cardiac edema: "Edema develops in chronic congestive failure because the kidneys do not excrete salt and water in a normal manner. This disturbance in renal function is related to the decreased cardiac output and not to engorgement of the kidneys from an increased venous pressure because the salt and water retention may occur before there is a rise in venous pressure." In our study, we have attempted to see also whether the venous pressure or the weight rose first as a patient went into cardiac decompensation; but instead of adding excess salt to induce failure, digitalis was withdrawn.

The Effect of Withdrawing Digitalis on Venous Pressure and Edema Formation.—Observations were made on three patients with clinically inactive rheumatic heart disease and chronic auricular fibrillation. Two of the patients (N. C. and L. B.) had both aortic and mitral valvular lesions, while the third (B. H.) had mitral stenosis and insufficiency. All three of the subjects had had repeated episodes of cardiac decompensation, with both left and right heart failure. In two of them peripheral edema had been present, while in the third (N. C.) no clinically detectable edema but marked enlargement of the liver and elevated venous pressure was observed during the periods of right heart failure.

When admitted to the hospital the patients were suffering from chronic heart failure of a moderate degree. Cardiac compensation was achieved by the use of digitalis and a diet which contained approximately 3 to 4 Gm. of sodium chloride a day. Absolute bed rest was not enforced, the patients being allowed a moderate amount of activity.

The venous pressure was measured in the basal state by the direct method, the level of the right auricle being estimated to be at a level 10 cm. above the back.⁸ The apical rate and the pulse rate were counted, and then the patient's weight was measured.

When clinical evidence and laboratory tests showed that cardiac compensation had been restored, cardiac failure was induced by omitting digitalis medication. Determinations of the venous pressure and of the weight were continued as during the control period.

The data obtained are listed in Table I and Fig. 1. Our results show that after the discontinuance of digitalis a considerable rise of venous pressure (approximately 60, 55, 85 mm. of water) occurred with no or very slight gain in weight. In Patient N. C. there was even a loss of weight which undoubtedly was due to the fact that he started to vomit a few hours before the termination of the experiment. The largest weight gain, 0.8 kilogram, occurred in Patient L. B. In this patient the venous pressure, after a considerable rise, fell spontaneously. Consequently a general diet was substituted for the salt-poor diet, which represented an increase of approximately 5 Gm. of sodium chloride a day. Following this change the venous pressure rose from 122 to 215 mm. of water during the next five days, while the patient's weight increased by only 0.9 kilogram. During the next four days the patient gained another 1.9 kilograms, while the venous pressure remained essentially unchanged. Only after this period did very slight pretibial edema appear.

TABLE I. THE EFFECTS OF STOPPING DIGITALIS IN THREE PATIENTS WITH HEART FAILURE

PATIENT	DATE	WEIGHT (KG.)	VENOUS PRESSURE (MM. OF WATER)	APICAL RATE	RADIAL RATE	REMARKS
B. H.	3/16	54.5	76	62	62	Taken off digitalis
	3/17	53.9	82			
	3/18	54.4	86	68	68	
	3/19	53.7				
	3/20	54.0	105			
	3/21	54.5	106	72		At 10 p.m. onset of fast au- ricular fibrillation and left heart failure; digitalized
	3/22	54.0	105	70		
	3/23	54.6	144	74		
	3/24	54.7	137	80		
N. C.	4/19	52.8	120	64	64	Taken off digitalis
	4/20	53.3	117	57	57	
	4/22					
	4/24	53.5	140	64	64	
	4/25	53.1	145			
	4/26	53.5	120	71	71	Vomiting; liver enlarged; digitalized
	4/27	53.3	140	72	72	
	4/28	53.2	131	67	67	
	4/29	53.3	150	88	84	
	4/30	52.2	173	140		
	5/1	51.7	83	80	80	
L. B.	6/22	40.3	89	60	60	Taken off digitalis
	6/23	40.3	82	45	45	
	6/25	40.4	95	62	62	
	6/26	40.0	108	64	64	
	6/27	40.0	108	62	62	
	6/29	40.3	124	58	58	7/22 put on general diet
	6/30	40.4	124	58	58	
	7/1	40.7	132	58	58	
	7/2	41.1	170	60	60	
	7/4		165	62	62	
	7/6	40.9	150	58	58	
	7/8	41.2	155	60	60	
	7/10	41.2	153	60	60	
	7/13	40.8	140	58	58	
	7/20	40.5	122	60	60	
	7/23	40.9	152	60	60	
	7/25	41.2	171	62	62	
	7/27	41.4	215	68	68	
	7/30	42.8	220	82	78	
	8/1	43.3	210	92	78	
						Moist râles over lung bases; slight pretibial edema; di- gitalized

It seems quite clear that when digitalis is withdrawn the first change noted is a rise in venous pressure before there is any significant weight gain. The three subjects all were patients with mitral stenosis and auricular fibrillation, and the objection may be raised that the sequence of events observed holds true only for patients with similar abnormalities. If this were true, we would have to formulate a different explanation of cardiac failure in each separate type of heart disease.

The data presented by Warren and Stead¹⁵ are open to some criticism. Their first patient was started on salt at a time when his hematocrit reading was 54 to 55. It seems quite possible that this patient was dehydrated. When his salt intake was increased and diuretics omitted, the hematocrit reading fell. After an hematocrit reading of 46 was reached, the weight and venous pressure rose simultaneously. The weight gained at the onset of the experiment may well have been the result of replacement of water and salt in a dehydrated person. In their second patient, the amount of weight gained before rise in venous pressure was 2.6 kilograms, since the first venous pressure reading recorded after this weight level was reached showed a rise from 40 to 150 mm. of water.

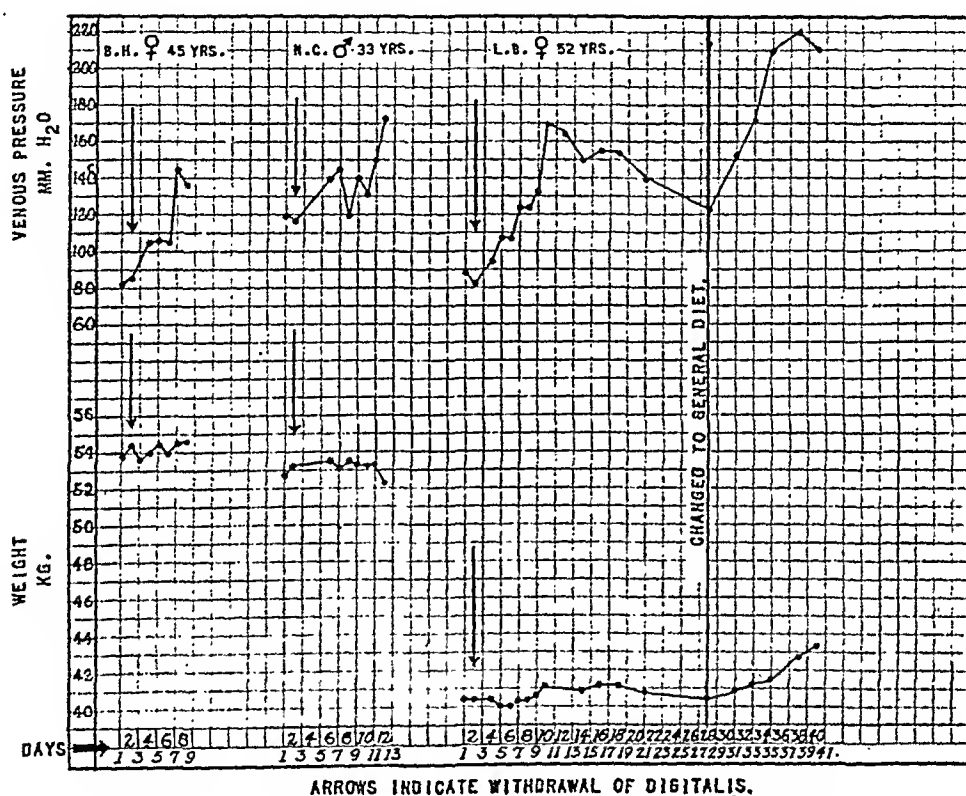


Fig. 1.—Changes in venous pressure and weight during development of cardiac failure.

Futcher and Schroeder⁵ in their experiments on the excretion of injected hypertonic sodium chloride in patients who had been in congestive heart failure studied also the changes in venous pressure. Of their five cases studied, adequate venous pressure readings were made on three patients. Of these, only two are suitable for discussion here because the venous pressure was at an abnormal level in the third patient at the onset of the experiment. In the first patient twenty-four hours after the administration of 33 Gm. of sodium chloride the venous pressure had risen 50 mm. of water (125 to 175) without weight gain. The second patient showed a rise in venous pressure of 43 mm. of water (115 to 158) and a weight gain of 1.5 kilograms twenty-four hours after the injection of 24 Gm. of sodium chloride. Thus we see that both of these patients studied by Futcher and Schroeder⁵ had a rise in venous pressure to abnormal levels with little or no weight gain.

L. B., our third subject, also showed a marked rise in venous pressure before gain in weight after salt had been added to her diet.

These observations are quite compatible with the backward failure hypothesis⁷ according to which cardiac edema is due mainly to the increased venous pressure secondary to right heart failure.

CONCLUSIONS

1. As cardiac decompensation develops after the withdrawal of digitalis, the rise in venous pressure precedes the gain in weight and the formation of edema.

2. The main factor in the production of cardiac edema is the increase in venous pressure.

The authors are deeply indebted to Dr. Tinsley R. Harrison for his guidance and suggestions throughout this study.

REFERENCES

1. Brankamp, R. G.: The Protein Content of Subcutaneous Edema Fluid in Heart Disease, *J. Clin. Investigation* 14: 34, 1935.
2. Fishberg, A. M.: Heart Failure, Philadelphia, 1940, Lea & Febiger.
3. Fremont-Smith, F.: Mechanism of Edema Formation, *New England J. Med.* 206: 1286, 1932.
4. Fremont-Smith, F.: The Mechanism of Water Diuresis in Man, *Proc. Soc. Clin. Investigation* 9: 7, 1930.
5. Futcher, P. H., and Schroeder, H. A.: Studies on Congestive Heart Failure. II. Impaired Renal Excretion of Sodium Chloride, *Am. J. M. Sc.* 204: 52, 1942.
6. Gibson, J. G., Jr., and Evans, W. A.: Clinical Studies of the Blood Volume. III. Changes in Blood Volume, Venous Pressure, and Blood Velocity Rate in Chronic Congestive Heart Failure, *J. Clin. Investigation* 16: 851, 1937.
7. Harrison, T. R.: Failure of the Circulation, ed. 2, Baltimore, 1939, Williams & Wilkins Co.
8. Kennedy, J. A., Lyons, R. H., and Burwell, C. S.: Measurement of Venous Pressure by Direct Method, *AM. HEART J.* 16: 675, 1938.
9. Krogh, A., Landis, E. M., and Turner, A. H.: Movement of Fluid Through Human Capillary Wall in Relation to Venous Pressure and Colloidal Osmotic Pressure of Blood, *J. Clin. Investigation* 11: 63, 1932.
10. Payne, S. A., and Peters, J. P.: Plasma Proteins in Relation to Blood Hydration; Serum Proteins in Heart Disease, *J. Clin. Investigation* 11: 103, 1932.
11. Smirk, F. H.: Observations on the Causes of Edema in Congestive Heart Failure, *Clin. Sc.* 2: 317, 1936.
12. Starling, E. H.: On the Absorption of Fluids From the Connective Tissue Spaces, *J. Physiol.* 19: 312, 1896.
13. Stead, E. A., Jr., and Warren, J. V.: The Protein Content of the Extracellular Fluid in Normal Subjects After Venous Congestion and in Patients With Cardiac Failure, Anoxemia, and Fever, *J. Clin. Investigation* 23: 283, 1944.
14. Thomson, W. A. R.: Plasma Proteins in Cardiac Edema, *Quart. J. Med.* 3: 587, 1934.
15. Warren, J. V., and Stead, E. A., Jr.: Fluid Dynamics in Chronic Congestive Heart Failure, *Arch. Int. Med.* 73: 138, 1944.

CORONARY SINUS RHYTHM

DAVID SCHERF, M.D., AND RAYMOND HARRIS, M.D.

NEW YORK, N. Y.

IT IS now generally accepted that stimuli originating in the auriculoventricular node may produce three patterns of cardiac rhythm. In the first type the pacemaker is situated in the upper part of the auriculoventricular node, and a normal or slightly shortened P-R interval occurs. In the second type the focus of origin is in the center of the node and both auricle and ventricle contract simultaneously. In the third type the stimulus originates in the lower part of the auriculoventricular node and the auricle is activated after the ventricle. Electrocardiograms imitating these three forms of auriculoventricular rhythm may also be found with the same focus of origin in the presence of conduction disturbances from the auriculoventricular node to the auricle or ventricle.^{13,26}

In the era before electrocardiography, the existence of auriculoventricular rhythm with a normal P-R interval caused much confusion. The appearance of normal auriculoventricular succession following extirpation of the sinus node even led some authors to assume that the sinus node was not the only pacemaker in the auricle under normal conditions. Later it was shown that, with an electrocardiogram exhibiting deeply inverted P waves in Leads II and III and a normal or only slightly shortened P-R interval, the focus of origin of the stimulus was situated in the upper part of the auriculoventricular node which extends to the sinus of the coronary vein. This rhythm was called coronary sinus rhythm.³⁰ This type of disturbance is still not too well known and has not yet been studied on an extensive basis.

In this paper we are reporting our observations on thirty-one patients with coronary sinus rhythm studied over a period of six years. The data obtained in our thirty-one cases are reproduced in Table I.

OBSERVATIONS

Incidence.—Between the years 1940 and 1945, inclusive, 23,610 electrocardiograms were taken at the Metropolitan Hospital where they were routine on the medical service. This figure includes many instances in which tracings were obtained repeatedly from the same patient. During this period, the electrocardiographic pattern of coronary sinus rhythm was observed in thirty-one patients, of which seventeen were men and fourteen were women. These

From the Medical Department of the New York Medical College, Metropolitan Hospital Service.
Received for publication March 23, 1946.

TABLE I. CLINICAL AND ELECTROCARDIOGRAPHIC FINDINGS IN THIRTY-ONE PATIENTS WITH CORONARY SINUS RHYTHM

CASE	NAME	SEX	AGE	FORM OF P WAVES IN LEAD					CLINICAL DIAGNOSIS	RATE	P-R INTERVAL DURING		OTHER ECG. CHANGES	REMARKS
				I	II	III	CR ₂	CR ₄			CSR	RSR		
1	G. E.	M	67	Low	Deeply neg.	Deeply neg.	Neg.	Neg.	Coronary sclerosis	77	0.17	0.20	Bundle branch block	Amyl nitrite and exercise cause only increased rate
2	J. F.	M	45	Low	Neg.	Neg.	—	—	Bronchopneumonia	84	0.12	—	Normal	
3	A. M.	F	59	Low	Neg.	Neg.	—	Diphasic	Posterior wall infarction	72	0.12	0.18	Q-T ₁ pattern	Carotid pressure causes sinus rhythm
4	J. G.	F	70	Low	Neg.	Neg.	—	—	Hypertension; hemiplegia	66	0.12	0.12	QRS slurred; T waves abnormal; depressed S-T _{1, 2}	Carotid pressure causes slowing; amyl nitrite causes acceleration and rare sinus escape
5	A. L.	M	19	Low	Neg.	Neg.	—	—	Bronchiectasis	62	0.13	—	Normal	
6	A. G.	F	40	Absent	Deeply neg.	Deeply neg.	—	—	Hypertension	100	0.10	—	Normal	
7	M. M.	F	29	Low	Deeply neg.	Deeply neg.	—	Neg.	Aortitis	88	0.13	—	Abnormal T waves in each lead	
8	R. D.	M	16	Low	Deeply neg.	Deeply neg.	—	—	Observation	71	0.12	0.14	Normal	
9	J. R.	M	22	Low	Neg.	Neg.	—	—	Keratitis	63	0.11	0.14	Normal	
10	G. W.	F	52	Low	Deeply neg.	Deeply neg.	—	Deeply neg.	Hypertension	110	0.08	—	Left ventricular strain pattern	

11	W. L.	M	63	Low	Deeply neg.	Deeply neg.	Deeply neg.	—	Deeply neg.	Hypertension	68	0.08	—	Inverted T ₁ ; no T ₂	
12	F. L.	F	31	Wide; positive	Deeply neg.	Deeply neg.	Deeply neg.	—	—	Rheumatic mitral lesion	120	0.16	—	Right axis deviation; no T waves	
13	G. M.	F	40	Invisible	Deeply neg.	Deeply neg.	Deeply neg.	—	Positive	Coronary sclerosis	98	0.13	—	QRS slurred; no abnormal T waves	
14	C. S.	M	68	Invisible	Deeply neg.	Deeply neg.	Deeply neg.	—	Positive	Coronary sclerosis; diabetes	66	0.15	0.15	Very low T ₁ ; multiform ventricular extrasystoles	
15	M. T.	M	56	Low	Neg.	Neg.	Neg.	—	—	Hypertension	56	0.12	0.16	Left ventricular strain pattern	Coronary sinus rhythm appears during carotid pressure
16	J. G.	M	68	Low	Deeply neg.	Deeply neg.	Deeply neg.	—	—	Coronary sclerosis; hypertension	96	0.14	0.20	QRS slurred; abnormal T waves	Changes to sinus rhythm from coronary sinus rhythm spontaneously; amyl nitrite and carotid pressure cause sinus rhythm
17	M. D.	F	76	Low	Deeply neg.	Deeply neg.	Deeply neg.	—	—	Pneumonia	106	0.12	0.20	Abnormal T waves in each lead	Carotid pressure causes sinus rhythm; amyl nitrite accelerates coronary sinus rhythm
18	Z. C.	F	80	Invisible	Deeply neg.	Deeply neg.	Deeply neg.	—	—	Coronary sclerosis	84	0.11	—	T ₁ abnormally low	Carotid pressure causes slowing; no other change
19	S. S.	M	24	Invisible	Deeply neg.	Deeply neg.	Deeply neg.	—	—	Observation	58	0.16	—	Right axis deviation	Exercise and amyl nitrite cause sinus rhythm
20	E. T.	F	45	Low	Deeply neg.	Deeply neg.	Deeply neg.	—	—	Hypertension	74	0.11	0.15	Left ventricular strain pattern	
21	G. D.	M	49	Low	Neg.	Neg.	Neg.	—	—	Rheumatic mitral lesion	72	0.14	0.18	Intraventricular block	

TABLE I. CLINICAL AND ELECTROCARDIOGRAPHIC FINDINGS IN THIRTY-ONE PATIENTS WITH CORONARY SINUS RHYTHM—CONT'D

CASE	NAME	SEX	AGE	FORM OF P WAVES IN LEAD					CLINICAL DIAGNOSIS	RATE	P-R INTER- VAL DURING		OTHER ECG. CHANGES	REMARKS
				I	II	III	CR ²	CR ⁴			CSR	RSR		
22	S. F.	M	62	Low	Neg.	Neg.	—	—	Coronary sclerosis	66	0.11	—	Left ventricular strain pattern	Carotid pressure, amyl nitrite, and exercise alter rate only
23	L. D.	M	36	Low	Neg.	Neg.	—	—	Rheumatic mitral lesion	100	0.12	—	Normal	
24	R. G.	F	41	Low	Neg.	Neg.	—	Isoelectric	Hypertension	90	0.09	—	Left ventricular strain pattern	
25	A. P.	F	52	Low	Neg.	Neg.	—	—	Hypertension; coronary sclerosis	100	0.12	0.12	Left ventricular strain pattern	Sinus escape
26	J. R.	M	72	Low	Neg.	Neg.	—	—	Senile emphysema	66	0.12	0.14	Normal	
27	D. O'K.	M	45	Low	Neg.	Neg.	—	—	Hypertension	60	0.15	—	Normal	
28	B. P.	F	63	Low	Neg.	Neg.	—	—	Hypertension	72	0.14	—	Intraventricular block	Marked depression of S-T _{1,2}
29	M. O'C.	F	74	Low	Deeply neg.	Deeply neg.	—	—	Hypertension	100	0.13	—	Marked depression of S-T _{1,2}	
30	J. L.	M	68	Low	Deeply neg.	Deeply neg.	—	—	Hypertension	82	0.15	—	Left ventricular strain pattern	
31	B. C.	M	70	Low	Neg.	Neg.	—	—	Coronary sclerosis	110	0.14	—	Abnormal T waves in each lead; low QRS complexes	

figures do not permit calculation of the true incidence of coronary sinus rhythm, but they do permit the conclusion that the condition is not as rare as was formerly believed. In another series of 10,000 cases, an auriculoventricular nodal rhythm was found in forty-five patients. Fifteen of these showed coronary sinus rhythm.²⁰ The incidence of coronary sinus rhythm is, therefore, approximately the same in these two series.

Electrocardiographic Pattern.—For many years, the form of the P waves in tracings of auriculoventricular rhythm was merely mentioned as being negative, and even in the classic monographs by Lewis¹⁵ and by Wenckebach and Winterberg²⁸ the form of the P waves in all three standard leads was not discussed.

It is now established that in auriculoventricular nodal rhythm the P wave in Lead I is low, positive, and sometimes invisible, while in Leads II and III it is negative.²⁹ In this paper are included only those tracings which show such P waves. Electrocardiograms with a positive P wave in Lead I, an inverted P wave in Lead III, and an isoelectric P wave in Lead II are not included since in these cases we are usually dealing with a regular sinus rhythm.

Another characteristic of the P waves frequently found in Leads II and III is their very sharply peaked form. Even when they have a duration of 0.05 second, the P waves seem shorter because they are so pointed. In the majority of our cases, we could not find the form showing a steep downstroke and a slow upstroke described as characteristic by Lewis.¹⁵ In the chest leads (CR₂ and CR₄) the form of the P waves usually resembles that found in Leads II and III, but diphasic as well as positive P waves were also observed.

In cases of coronary sinus rhythm the electrical axis of the auricle points to the left and the depolarization of the auricle proceeds in a direction opposite to that occurring under normal conditions.^{19,21}

The electrocardiogram reproduced in Fig. 1, obtained from a patient with syphilitic aortitis and involvement of the coronary artery orifices, shows P waves that are positive in Lead I and sharply inverted in Leads II, III, and CR₄. The P-R interval measures 0.11 second. There is moderate right-axis deviation. The abnormal depression of the S-T segment is partly due to digitalis treatment.

With slight variations, the P wave pattern described previously was seen in all cases. In seventeen tracings, the sharp pointing was present. The P waves in a case of mitral stenosis were markedly widened, but even here the negative pointing in Leads II and III was present despite the intra-auricular conduction disturbance.

The P-R interval during coronary sinus rhythm varied between 0.08 and 0.17 second. Tracings with a P-R interval of less than 0.08 second were not included in this investigation. In one case the P-R interval during coronary sinus rhythm was 0.17 second, and during regular sinus rhythm it was 0.20 second (Case 1, Table I). In fourteen electrocardiograms the P-R interval during coronary sinus rhythm measured between 0.10 and 0.12 second. In thirteen cases it was possible to compare in the same individual the P-R interval during regular sinus rhythm with that found during coronary sinus rhythm. The difference between both values ranged from 0.0 to 0.08 second. In three patients the

P-R interval was found to be the same during both rhythms. It is important in evaluating these figures to re-emphasize that the length of the P-R or R-P interval during auriculoventricular rhythm depends not only upon the position of the stimulus formation center in the auriculoventricular node, but also upon the speed of conduction from this center up to the auricle and down to the ventricle.

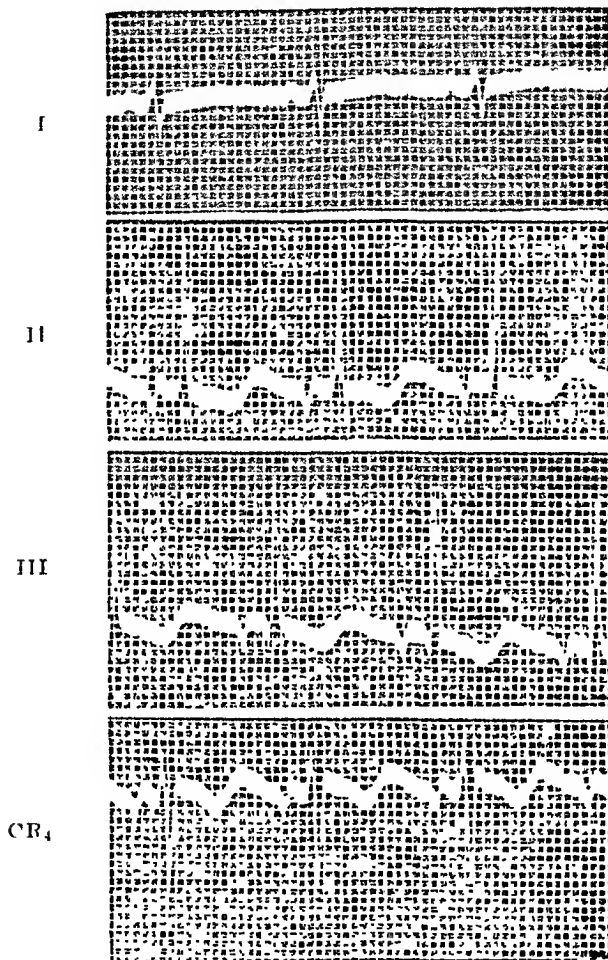


Fig. 1.—Coronary sinus rhythm with right-axis deviation and abnormal S-T segments and T waves.

The heart rate during coronary sinus rhythm varied between 56 and 120 beats per minute. No relation could be detected between the heart rate and the length of the P-R interval.

Evidence of myocardial damage was found in the electrocardiograms of twenty-three patients. In two of these patients right-axis deviation was present. The electrocardiogram was normal in eight patients.

Condition of the Heart.—Clinical evidence of organic heart involvement was present in twenty-four patients. In thirteen of these, hypertension was observed. Marked abnormalities in the electrocardiogram, cardiac enlarge-

ment, or other signs in the other eleven patients indicated the presence of an abnormal heart usually due to coronary sclerosis. In some elderly patients or in patients with pneumonia, the presence of organic changes in the heart was possible despite normal clinical findings. The heart was presumably normal on clinical and electrocardiographic examinations in only three subjects (Cases 5, 8, and 9, Table I).

In connection with our data, it is worthy of emphasis that Ruskin and his associates found ten patients with definite evidence of heart disease among fifteen cases of coronary sinus rhythm.²⁰ Hypertension was present in eight of the ten cases. In another series of twelve patients with different types of auriculoventricular nodal rhythm, seven showed hypertension.⁹

Response to Exercise, Amyl Nitrite Inhalation, and Carotid Sinus Pressure.—One feature of the coronary sinus rhythm is its lability. Capable of changing spontaneously, coronary sinus rhythm may frequently also be converted easily into regular sinus rhythm by exercise, amyl nitrite inhalation, or carotid sinus pressure. This change, of course, is possible only in those cases where the sinus node still functions. In some cases exercise or inhalation of amyl nitrite simply causes acceleration of the existing coronary sinus rhythm (Table I); in others, these measures cause the sinus rhythm to become so accelerated that it gains the upper hand and displaces the coronary sinus rhythm. The results cannot be predicted because they depend on the degree of acceleration of either node.

Similarly, pressure on the right or left carotid sinus may only slow the existing coronary sinus rhythm or change either rhythm into the other. In Fig. 2 is shown the effect of right carotid pressure in Lead III of the electrocardiogram on a patient who displayed coronary sinus rhythm spontaneously on many occasions. The rate was slowed; one beat with an abnormal P wave presumably was caused by one part of the auricle being activated by the sinus node and another part by the auriculoventricular node; then pure coronary sinus rhythm followed. Once established, this abnormal rhythm often persisted for a long time with a rate frequently the same as that of the regular sinus rhythm preceding the carotid pressure.

In Fig. 3 is shown a spontaneous change in Lead II from coronary sinus rhythm to regular sinus rhythm and back to coronary sinus rhythm. In many instances the changes, resembling the sudden ending of a paroxysmal tachycardia, are as abrupt as in the beginning of Fig. 3.

Sinus Escape.—During auriculoventricular rhythm in dogs caused by cooling of the sinus node, an "escape" of the sinus node in the form of normal beats with normal P waves and normal P-R intervals was observed occasionally.^{14,16} Some of these tracings were explained in a different way,²⁶ but a sinus escape undoubtedly occurs. We were able to observe it in the electrocardiograms of three patients.

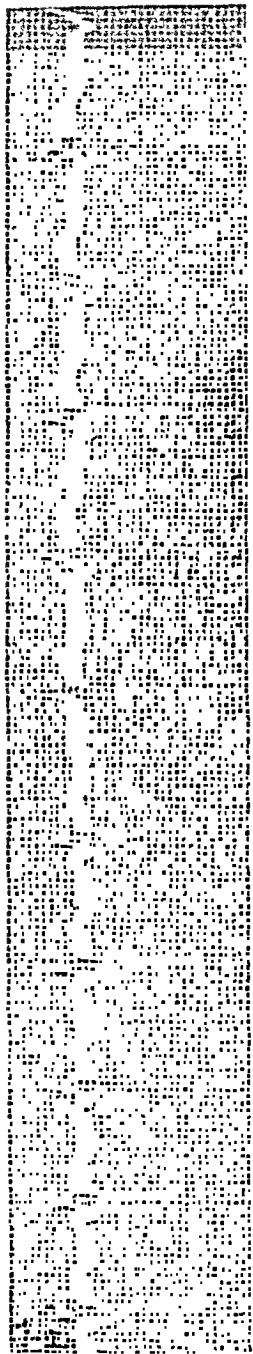


Fig. 2.—Lead III. Right carotid pressure changes sinus rhythm into coronary sinus rhythm.

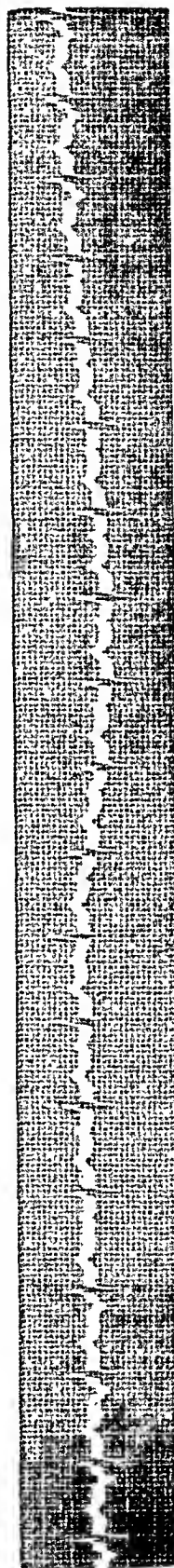


Fig. 3.—Lead II. Spontaneous change from coronary sinus rhythm to sinus rhythm and back to coronary sinus rhythm.

Fig. 4 was obtained from Case 1, Table I. A left bundle branch block is present and the P waves show the typical sharp inversion in Leads II and III. In Lead II, as well as in CR₂, slightly premature beats with normal P waves and somewhat longer P-R intervals occasionally appear. Their interpretation as sinus escape beats seems justified.

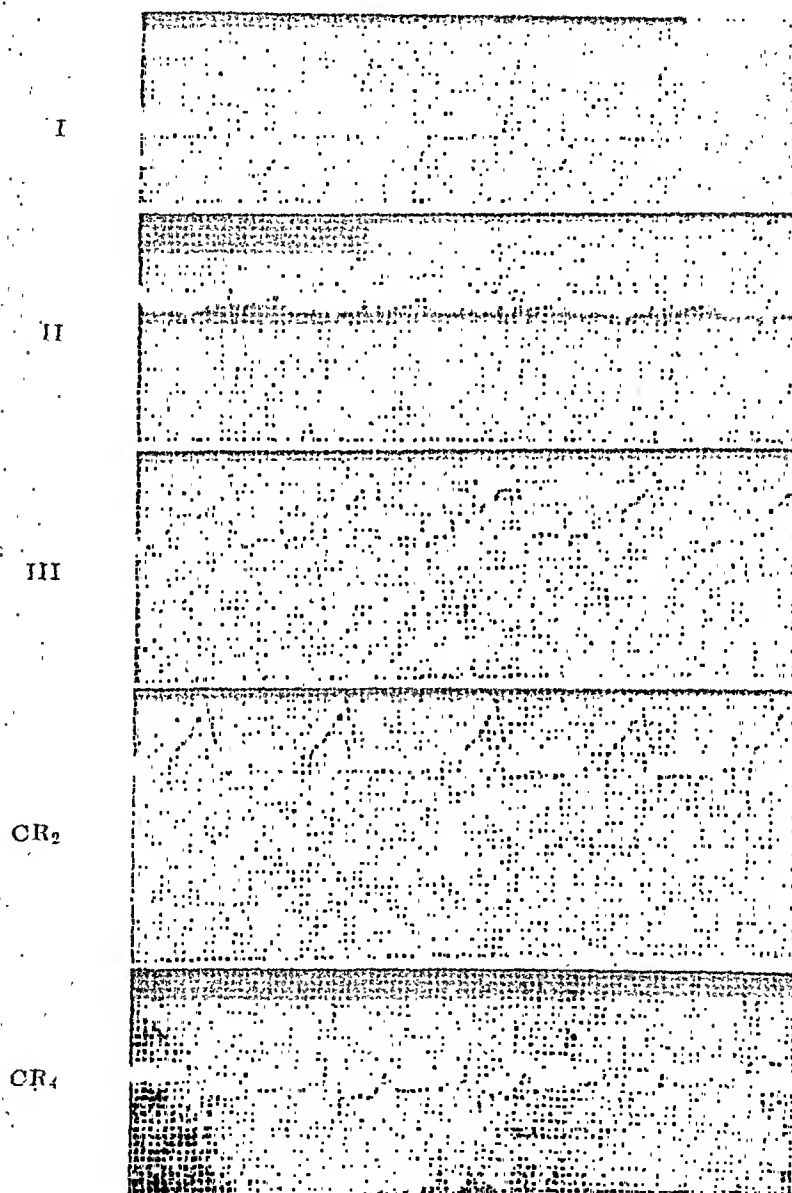


Fig. 4.—Coronary sinus rhythm with sinus escape in Leads II and CR₂.

DISCUSSION

The diagnosis of coronary sinus rhythm in tracings like those of Figs. 1 to 4 is supported by the result of anatomic and experimental investigations. Anatomic observations reveal data compatible with the assumption that the coronary sinus area is occasionally the site of stimulus formation. In his classic treatise, Tawara described specific fibers which enter the posterior part of the auriculo-ventricular node from the sinus of the coronary vein.²⁷ The characteristic struc-

ture of the specific fibers near the coronary sinus in the calf was described by Aschoff who was reminded of a third stimulus center in addition to the sinus and auriculoventricular nodal centers.²

The specific muscle fibers of the auricle which originally formed one unit are later separated into two parts, one which represents the sinus node, and a second which unites with the auriculoventricular node to form its auricular portion.¹ The peculiar structure of the coronary sinus fibers was also stressed by others.^{11,12} Kung described a small bundle of muscle fibers entering the auriculoventricular node from the area of the coronary sinus. This bundle contained many ganglion cells which in several places were in direct contact with the muscle fibers. A network of nerve fibers also surrounded the muscle fibers. From these findings, the author concluded that these structures apparently possessed a remarkable functional ability.¹²

Experimental work showed that warming of the coronary sinus area in dogs caused a tachycardia with a normal P-R interval.³⁰ In dogs exhibiting electrocardiograms with inverted P waves preceding the QRS complex by a normal distance, the area of primary negativity (the focus of stimulus formation) has been found to be in the coronary sinus area by direct leads.¹⁷ In the experiments by Zahn, however, only smoked paper tracings were used, and doubts were expressed concerning the results of his experiments and the studies of Meek and Eyster.¹⁴ Therefore, the experiments of Zahn were repeated with the aid of the electrocardiogram.²⁴ It could be shown that a regular tachycardia with deeply inverted P waves and normal P-R intervals occurred during the warming of the coronary sinus area through the wall of the coronary vein or inferior caval vein in the dog heart in situ.

Since an electrocardiogram with three limb leads obtained in such an experiment has never been reproduced to our knowledge, one of these experiments may be described here. Fig. 5 was obtained from a dog weighing 4.45 kilograms. During artificial respiration, the chest wall and pericardium were opened under nembutal and morphine anesthesia. The apical area of the heart was slightly lifted from its pericardial bed and a thermode was applied through the wall of the inferior caval vein to the area around the orifice of the coronary sinus.

Lead I, obtained after discontinuation of the warming of the coronary sinus, shows in the beginning a tachycardia caused by the warming of the coronary sinus area. The P waves are not clearly visible because they are low. With slowing of the heart rate, sinus rhythm with normal positive P waves recurs. Lead II, registered during the tachycardia, shows deeply inverted P waves followed by positive Ta waves and preceding the QRS complex by about 0.11 second. The tracing of Lead III, as in Lead I, was obtained after discontinuation of the warming process. In the first half of the tracing, deeply inverted P waves precede the QRS complex, but in the second half regular sinus rhythm recurs with high positive P waves and inverted Ta waves.

In all experiments, the same pattern of P waves was obtained as in the clinical tracings. In Lead I the P wave was invisible or low positive; in Leads II and III it was deeply inverted and usually sharply peaked.

In our opinion, coronary sinus rhythm is actually not as rare as it is often believed to be; then too, it is frequently overlooked. That inverted P waves appear under normal conditions in Lead III is known but when they were also found in Lead II, they were often not attributed to a new rhythm but rather explained by summation according to the Einthoven rule. Some authorities⁷ diagnose auriculoventricular rhythm even with isoelectric P waves in Lead II. For this study we accepted only cases with definitely inverted P waves in Leads II and III. In doubtful cases it will be of help to know that coronary sinus rhythm is extremely variable and that spontaneously, or with carotid pressure, or exercise, it changes readily into sinus rhythm.

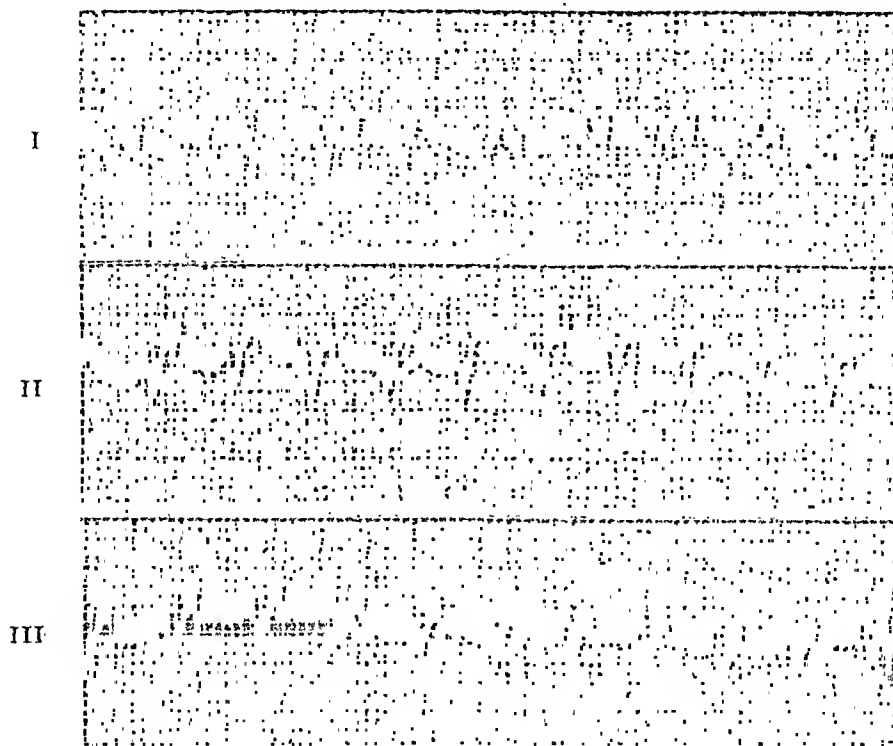


Fig. 5.—Coronary sinus rhythm produced experimentally in the dog. For description of the three limb leads, see text.

Only twice during the observation period of six years did we find the form of auriculoventricular rhythm with inverted P waves between QRS and T; that is, auriculoventricular rhythm originating in the lower node. Both times, this rhythm was temporary. Auriculoventricular rhythm without visible P waves, usually attributed to a stimulus originating in the middle of the auriculoventricular node, was seen only nine times. These results differ from those of other writers²⁰ who saw among 45 patients with auriculoventricular rhythm the merging of P waves with QRS complexes in twenty-four instances.

Since it is known that the automaticity of the specific fibers of the heart diminishes gradually from above downward,⁸ one would expect that the coronary sinus area, in view of the high automaticity of the coronary sinus fibers, is always next in line if the sinus node ceases to function and that this form of auriculo-

ventricular rhythm would occur more often. Actually, even in animal experiments which are more susceptible to analysis, the destruction of the sinus node is frequently followed by that form of auriculoventricular rhythm in which the auricle and ventricle contract simultaneously and not by coronary sinus rhythm as one might expect.

The fact that the coronary sinus area is in such close contact with nerve fibers and ganglion cells, and is so easily influenced by exercise, carotid pressure, and other factors, appears to us to offer the explanation. Since the vagus nerve exerts a greater chronotropic effect on the coronary sinus region than on the main part of the auriculoventricular node,⁸ it is clear that every factor which abolishes the action of the sinus node by vagal effects, such as carotid sinus pressure, digitalis, and reflexes,²² may also lead to inhibition of the activity of the coronary sinus. Under these circumstances, the pacemaker will be situated in the deeper parts of the auriculoventricular node, and both auricle and ventricle will be activated simultaneously. Moreover, even with stimulus formation in the coronary sinus area, the reversed conduction to the auricle may be prevented by a high vagal tonus so that electrocardiograms of these two forms would look alike.

Blocking of the reversed conduction to the auricle is the most probable reason why warming of the coronary sinus area in experiments on the Langendorff heart caused a rapid auriculoventricular rhythm without causing the P waves to become visible before the QRS complexes.²³ In such experiments, naturally normal conditions never prevail. It has been claimed that crushing of the specific fibers of the sinus node, thus abolishing its activity by strong stimuli, causes auriculoventricular rhythm with a positive P-R interval while stopping the activity of the sinus node by cooling leads to auriculoventricular rhythm in which auricle and ventricle contract simultaneously.⁴ These results were not confirmed.²³

Some confusion was introduced into the picture when some authors^{3,10,13} called electrocardiograms with positive P waves in each lead and P-R intervals of 0.12 second or less coronary sinus or coronary nodal rhythm. Such tracings, however, belong to a normal sinus mechanism,²⁰ and the short P-R interval must be attributed to other causes. It is frequently found in thiamine deficiency and is often seen in certain types of hypertension.²⁵ A shortened P-R interval with positive P waves and abnormal ventricular complexes is also seen in the Wolff-Parkinson-White syndrome, which is explained by an abnormal connection between auricle and ventricle.

The question arises as to whether or not one is justified in separating coronary sinus rhythm from the rhythm originating in the auricular portion of the auriculoventricular node. According to some authorities, definite shortening of the P-R interval would speak for upper auriculoventricular nodal rhythm while a normal P-R interval would permit the diagnosis of coronary sinus rhythm.²⁸ Table I shows, however, that the length of the P-R interval during coronary sinus rhythm will depend to a great degree on the length of the P-R interval during sinus rhythm in the respective patient. The P-R interval during coronary

sinus rhythm is often, but not always, slightly shorter than during regular sinus rhythm. With a P-R interval of 0.18 second during regular sinus rhythm, a P-R interval of 0.12 second or more may be found during coronary sinus rhythm. The condition of the auriculoventricular conduction system will influence the P-R interval during both rhythms.

In experimental work on dogs, the P-R interval during coronary sinus rhythm was shorter⁸ or longer³⁰ than during sinus rhythm. In the latter instance, a very rapid heart rate usually prevailed which may explain the prolongation. In eight experiments on dogs, the length of the P-R interval during both rhythms was compared²⁴ and was not found shorter when sinus rhythm changed into coronary sinus rhythm. Here, however, the rate during coronary sinus rhythm was also rapid. It appears, therefore, that until more is known about this rhythm, the question of separation of the coronary sinus rhythm from the "upper nodal rhythm" must be left open since the borderline between them is still not sharply defined.

Since the term, coronary sinus rhythm, may easily be confused with sinus rhythm, the problem arises as to whether another designation for the rhythm originating around the coronary sinus may not be preferable. Supranodal rhythm, a term proposed for the auriculoventricular rhythm in which the P wave precedes the QRS complex in a normal interval,⁵ may be considered as a possible synonym.

While coronary sinus rhythm is usually found in an abnormal heart, particularly in patients with coronary sclerosis and hypertension, it may occur in an otherwise apparently healthy person. A slight depression of the activity of the sinus node and a moderate acceleration of the coronary sinus centers may cause the abnormal rhythm.

CONCLUSIONS

Electrocardiographic and clinical observations made on thirty-one patients with coronary sinus rhythm are discussed.

Coronary sinus rhythm has a well-defined electrocardiographic picture with a normal or slightly shortened P-R interval, low positive or absent P waves in Lead I, and deep, inverted P waves, which are usually peaked, in Leads II and III.

A large majority of patients demonstrating this disturbance have evidence of an organic heart lesion.

The anatomic and physiologic peculiarities of the specific tissue around the orifice of the coronary sinus vein are discussed.

Differentiation between the rhythm originating in the area of the coronary sinus and the rhythm originating in the upper part of the auriculoventricular node is not yet possible.

REFERENCES

1. Aschoff, L.: Discussion, Deutsche med. Wchnschr. 40: 1036, 1914.
2. Aschoff, L.: Die Herzstoeurungen in ihrer Beziehung zum spezifischen Muskelsystem des Herzens, Centralbl. f. allg. Path. u. path Anat. 21: 433, 1910.
3. Borman, M. C., and Meek, W. J.: Coronary Sinus Rhythm, Arch. Int. Med. 47: 957, 1931.
4. Brandenburg, K., and Hoffman, P.: Wo entstehen die normalen Bewegungsreize im Warmblüterherzen und welche Folgen für die Schlagfolge hat ihre reizlose Ausschaltung? Med. Klin. 8: 16, 1912.
5. Clerc, A., and Pezzi, L.: Le rythme septal du coeur, Arch. dmal. du coeur. 13: 103, 1920.
6. Cohn, A. E., Kessel, L., and Mason, H. H.: Observations on the Functions of the Sino-Auricular Node in the Dog, Heart 3: 311, 1911.
7. Danielopolu, D., and Proca, G. G.: Recherches sur le rythme atrioventriculaire chez l'homme, Arch. dmal. du coeur 19: 247, 1926.
8. Eyster, J. A. E., and Meek, W. J.: Studies on the Origin and Conduction of the Cardiac Impulse, An. J. Physiol. 61: 117, 1922.
9. Flaxman, N.: Atrioventricular Nodal Rhythm, Am. J. M. Sc. 201: 857, 1941.
10. Katz, L. N.: Electrocardiography, Philadelphia, 1941, Lea & Febiger.
11. Koch, W.: Ueber die Bedeutung der Reizbildungsstellen (kardiomotorischen Zentren) des rechten Vorhofes beim Säugetierherzen, Arch. f. d. ges. Physiol. 151: 275, 1913.
12. Kung, S. K.: Herzblockstudien, Arch. f. exper. Path. u. Pharmakol. 155: 295, 1930.
13. Langendorf, R., Simon, A. J., and Katz, L. N.: A-V Block in A-V Nodal Rhythm, AM. HEART J. 27: 209, 1944.
14. Lewis, T.: The Effect of Vagal Stimulation Upon Atrioventricular Rhythm, Heart 5: 247, 1913.
15. Lewis, T.: The Mechanism and Graphic Registration of the Heart Beat, ed. 3, London, 1925, Shaw & Sons.
16. Lewis T., and White, P. D.: The Effects of Premature Contractions in Vagotomised Dogs, With Special Reference to Atrioventricular Rhythm, Heart 5: 335, 1914.
17. Meek, W. J., and Eyster, J. A. E.: Experiments on the Origin and Propagation of the Impulse in the Heart, Heart 5: 227, 1914.
18. Miller, R. A.: Auriculo-Ventricular Rhythm, Brit. Heart J. 6: 107, 1944.
19. Ruskin, A., and Decherd, G.: Momentary Atrial Electrical Axes, AM. HEART J. 29: 633, 1945.
20. Ruskin, A., McKinley, W. F., and Decherd, G. M.: Studies of the A-V Node: IV. A Clinical Study of Atrioventricular Nodal Rhythm, Texas Rep. Biol. & Med. 3: 86, 1945.
21. Schellong, F.: Ueber die elektrokardiographische Bestimmung des Ausgangspunktes von Vorhofextrasystolen, München. med. Wchnschr. 73: 614, 1926.
22. Scherf, D.: Experimental Sinoauricular Block, Proc. Soc. Exper. Biol. & Med. 61: 286, 1946.
23. Scherf, D.: Ueber den atrioventriculären Rhythmus, Ztschr. f. d. ges. exper. Med. 78: 511, 1931.
24. Scherf, D.: Upper Auriculo-Ventricular Rhythm (Coronary Sinus Rhythm) Experimentally Produced, Proc. Soc. Exper. Biol. & Med. 56: 220, 1944.
25. Scherf, D.: The Short P-R Interval and Its Occurrence in Hypertension, Bull. New York M. Coll., Flower and Fifth Ave. Hosps. 4: 116, 1941.
26. Scherf, D., and Shookhoff, C.: Reizleitungsstörungen im Bündel, Wien. Arch. f. inn. Med. 10: 97, 1925.
27. Tawara, S.: Das Reizleitungssystem des Säugetierherzens, Jena, 1906, Gustav Fischer.
28. Wenckebach, K. F., and Winterberg, H.: Die unregelmässige Herztätigkeit, Leipzig, 1927, Wilhelm Engelmann.
29. Wilson, F. N.: Regular Ectopic Rhythms, J. Lab. & Clin. Med. 1: 476, 1915.
30. Zahn, A.: Experimentelle Untersuchungen ueber Reizbildung und Reizleitung im Atrioventrikularknoten, Arch. f. d. ges. Physiol. 151: 247, 1913.

ABNORMALITIES OF THE RESPIRATORY PATTERN IN PATIENTS WITH CARDIAC DYSPNEA

HOWARD E. HEYER, M.D.

DALLAS, TEXAS

INTRODUCTION

DETAILED analyses of the time relationships and variations in contour of respiratory tracings recorded by the Marey pneumograph have not been made in patients with cardiac dyspnea. Spirographic records of respiration in patients with dyspnea due to heart disease have been concerned only with rate and depth of breathing and not with variations in the relative duration of expiration and inspiration or with changes in form. Furthermore, since spirographic tracings employ a slowly moving cylinder, the records are closely compressed so that variations in contour are not easily detected, and accurate measurements of time relationships are difficult. By utilizing a rapidly moving drum, the pneumograph yields tracings which can easily be measured. The present study deals with an analysis of the time relationships of expiration and inspiration and of changes in contour recorded by such means. Observations were made on normal subjects as well as on patients with cardiac dyspnea and dyspnea due to allergic bronchial asthma. The changes produced by exercise and by the administration of aminophylline were also noted.

METHOD OF STUDY

A record of the chest movements during breathing were made with a Marey pneumograph which produced tracings on smoked paper on the rotating drum of a kymograph. Measurements were made by means of a caliper micrometer of (a) the total duration of individual breaths, (b) the duration of inspiration, and (c) the duration of expiration. The estimated respiratory rate for each breath was computed from the total duration of that cycle. Many breaths were thus measured at various intervals on each record. The value for the respiratory rate, the durations of inspiration and expiration in each breath, plus the numerical ratio of duration of expiration (in seconds): duration of inspiration (in seconds) were then expressed for each tracing. By this method of study, observations were made on normal subjects, patients with dyspnea and pulmonary congestion caused by heart failure, and patients with allergic bronchial asthma. Studies of the vital capacity were also made before and after administration of aminophylline (theophylline ethylenediamine) intravenously. The five normal subjects studied were medical students ranging in age from 20 to 25 years. They were free of any clinical evidence of cardiac or pulmonary disease; determinations of the circulation time (employing ether and decholin) and venous pressure were made and were found to be normal. Eleven patients with heart disease, ranging in age from 22 to 79 years, who were free of any history of allergic manifestations were studied (see Table I). Three of these patients suffered from syphilitic aortic insufficiency, four were diag-

From the Department of Internal Medicine, Southwestern Medical College, and the Medical Service of Parkland Hospital.

Received for publication Feb. 27, 1946.

nosed as having hypertensive heart disease and two as having arteriosclerotic heart disease, and two revealed evidence of mitral stenosis of rheumatic origin. All of these eleven subjects showed clinical and roentgenologic evidence of pulmonary congestion, with moist râles in the lung fields and, in several cases, with a definite wheezing type of expiration. All tracings were taken in the sitting position. The exercise in normal subjects consisted of forward bending from a standing position, touching the toes with the fingers forty times. In the patients with heart disease, a few were able to bend forward and touch the toes ten times, while in the remainder, swinging of the arms across the chest from ten to sixty times (depending on the capacity of the individual patient for exercise) was sufficient to produce a definite hyperpnea.

RESULTS

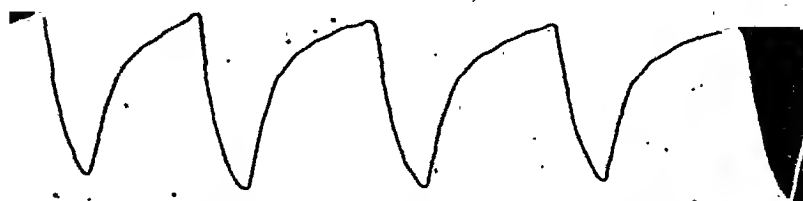
Normal Subjects at Rest.—In Fig. 1, *A*, is shown a typical tracing of a normal subject at rest. The great majority of tracings revealed a similarity of contour for each individual subject and the shape of the tracing tended to reproduce itself in the same patient, with some minor deviations. The inspiratory downstroke was typically very slightly concave and the expiratory upstroke very slightly convex (upward). The inspiratory phase tended to follow immediately after expiration without pause. The infrequency of the expiratory pause has been previously noted in an analysis of spirographic tracings by Caughey.¹ The total duration of each individual breath varied inversely with the respiratory rate, being shorter with a rapid rate and longer with a slow respiratory rate. The numerical relationship of the duration of expiration (in seconds) to the duration of inspiration (in seconds) varied, for the five subjects at rest, from 1.30:1 to 1.96:1 (Fig. 2). The average value for the expiratory:inspiratory ratio in the five normal subjects at rest was 1.61. Otherwise stated, this means that the average duration of expiration was 1.61 times as long as the average value for inspiration in these normal subjects. This is in close agreement with values found for this ratio by Mudd² by means of spirographic tracings.

Normal Subjects After Exercise.—Reference to Fig. 3*A* shows that after exercise the respiratory rate increased sharply and the duration of inspiration decreased somewhat, while the duration of expiration fell sharply. This decrease in the duration of expiration following exercise was of much greater magnitude than the decrease in the duration of inspiration. Fig. 3*B* reveals that the ratio, duration of expiration:duration of inspiration, also fell abruptly in the cycles immediately following exercise. After the subject recovered from his hyperpnea the duration of inspiration, expiration, and the expiratory:inspiratory ratio slowly returned toward resting values. The changes seen in Figs. 3*A* and 3*B* were found to be a constant pattern recurring after exercise in all of the five normal subjects. Reference to Fig. 2 will show that the average expiratory:inspiratory ratio for the group of normal subjects immediately after exercise was found to be 1.39:1. It will be seen from these data that the typical response to exercise in the normal subject was a selective shortening of the expiratory phase, and that it was mainly by shortening of this portion of each breath that the increase in respiratory rate occurred. The ease with which this change occurred indicated that there was, after exercise, both active participation of the muscles of expiration and an absence of any expiratory obstruction.

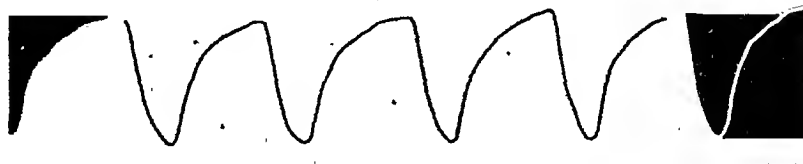
Patients With Heart Disease: Studies While Resting.—In Fig. 1, C and D, is shown a definite lengthening of the expiratory phase in resting patients with cardiac dyspnea. The tracings also were typified by an increase in upward convexity of the expiratory limb. The *relative* duration of the expiratory phase was



A - Resting normal subject.



B - Patient with allergic bronchial asthma.



C - Patient with severe cardiac asthma and expiratory wheezing.



D.- Patient with cardiac failure, pulmonary congestion and expiratory wheeze.



E - Same patient as in D, immediately after Theophylline with ethylene-diamine, .5 gm. i.v.

Fig. 1—Pneumographic tracings. Downstroke, inspiration; upstroke, expiration.

found to be considerably increased in all eleven patients with heart disease studied. Reference to Fig. 2 reveals that at rest the expiratory:inspiratory ratio gave definitely higher values than in the group of normal subjects. For the entire group the average expiratory:inspiratory ratio was found to be 2.17:1, with a range extending from 1.52 to 2.90. In any given patient, although fluctua-

tions occurred, the values were always found to fall in this range. This prolongation of the expiratory phase, with upward convexity of the expiratory limb, was most striking in the patients with frank cardiac asthma (Patients 1, 3, 4, and 7, Table I, and Patient C, Fig. 1) but was also seen in the other patients with heart disease who were free of the expiratory wheeze. These studies were interpreted as indicating that there is a definite relative prolongation of expiration in the patient suffering from cardiac dyspnea.

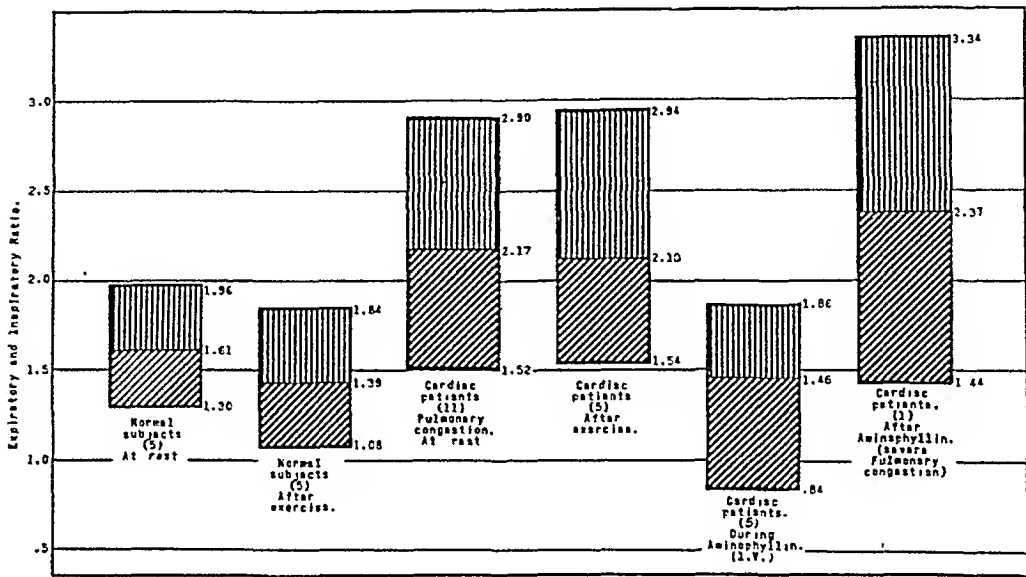


Fig. 2.—Expiratory:inspiratory ratio in normal subjects and patients with heart disease. Middle figure, mean for group; upper and lower figures, maximum and minimum range for group.

TABLE I. EXPIRATORY:INSPIRATORY RATIO OF PATIENTS WITH HEART DISEASE

PATIENT	DIAGNOSIS	AVERAGE EXPIRATORY:INSPIRATORY RATIO		
		AT REST	AFTER EXERCISE	AFTER AMINOPHYLLINE
1 (J. H.)	Syphilitic aortic insufficiency; cardiac asthma	2.69	2.54	1.56
2 (C. M.)	Hypertensive heart disease.....	1.94	1.77	1.26
3 (C. W.)	Rheumatic heart disease; mitral stenosis; cardiac asthma.....	2.03	2.18	1.60
4 (M. Y.)	Hypertensive heart disease; cardiac asthma.	2.38	2.00	—
5 (F. C.)	Syphilitic aortic insufficiency.....	2.00	—	1.55
6 (G. S.)	Hypertensive heart disease.....	2.03	2.00	1.50
7 (G. P.)	Hypertensive heart disease; cardiac asthma.	2.24	—	—
8 (J. J.)	Arteriosclerotic heart disease.....	2.07	—	—
9 (M. G.)	Arteriosclerotic heart disease.....	2.12	—	—
10 (M. J.)	Rheumatic heart disease; mitral stenosis...	1.96	—	—
11 (W. L.)	Syphilitic aortic insufficiency.....	2.30	—	—
Average expiratory:inspiratory ratio.....		2.17	2.10	1.46

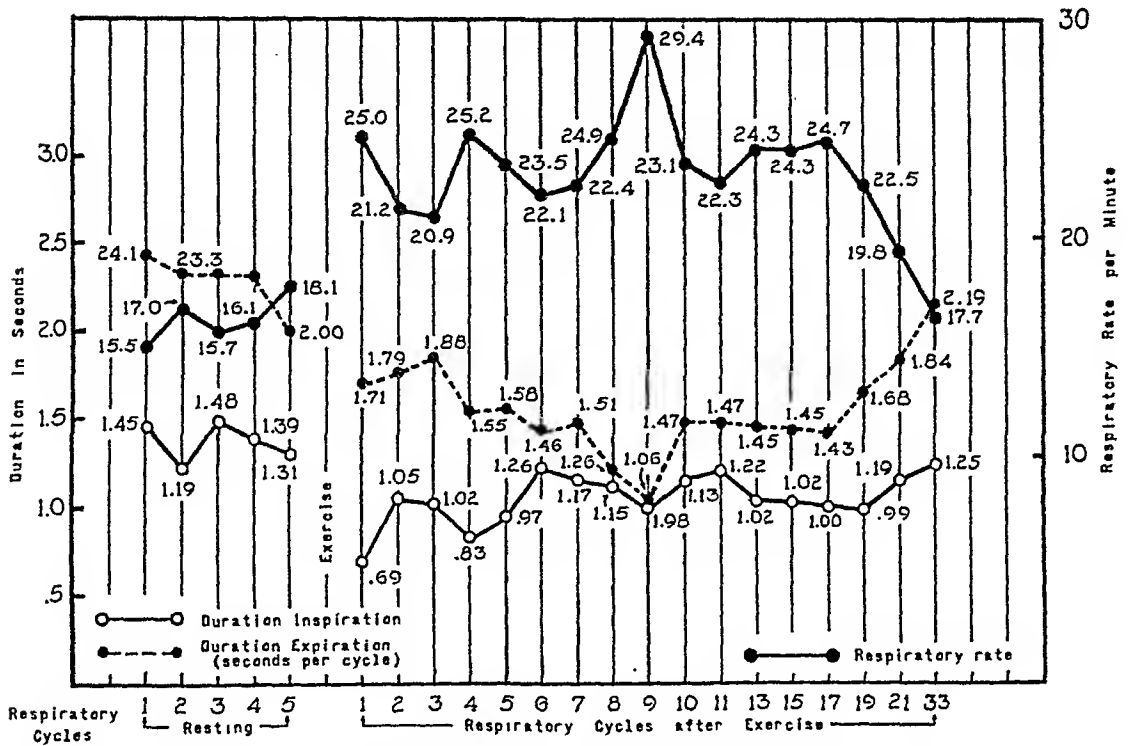


Fig. 3A.—Actual duration of expiration and inspiration (in seconds) per breath in normal subject (M. B.) at rest and after exercise.

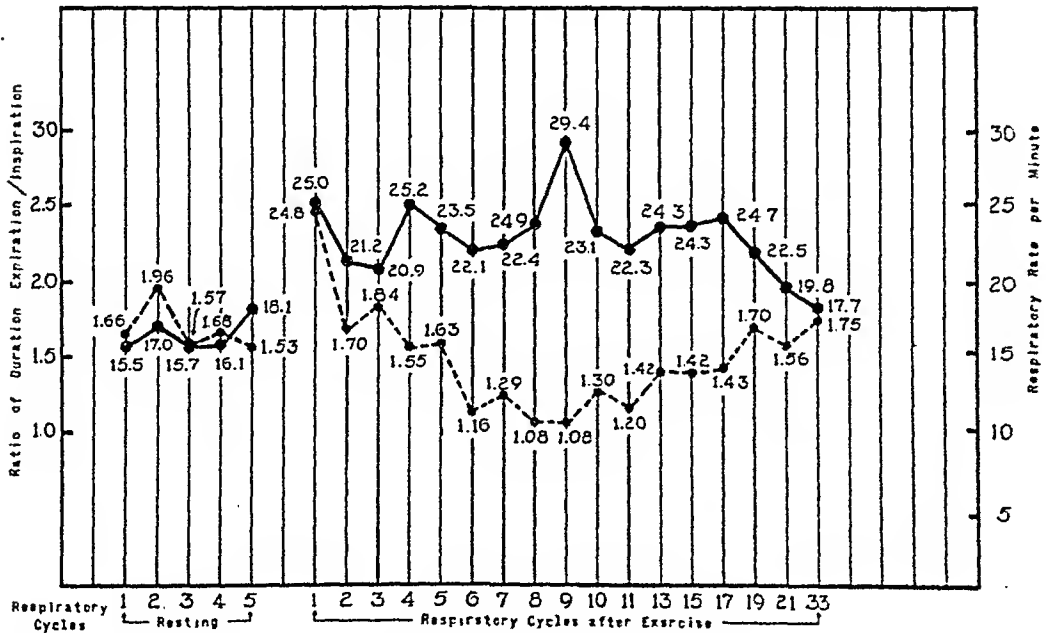


Fig. 3B.—Expiratory: inspiratory ratio for individual breaths of normal subject (M. B.) at rest and after exercise (same patient as in Fig. 3A).

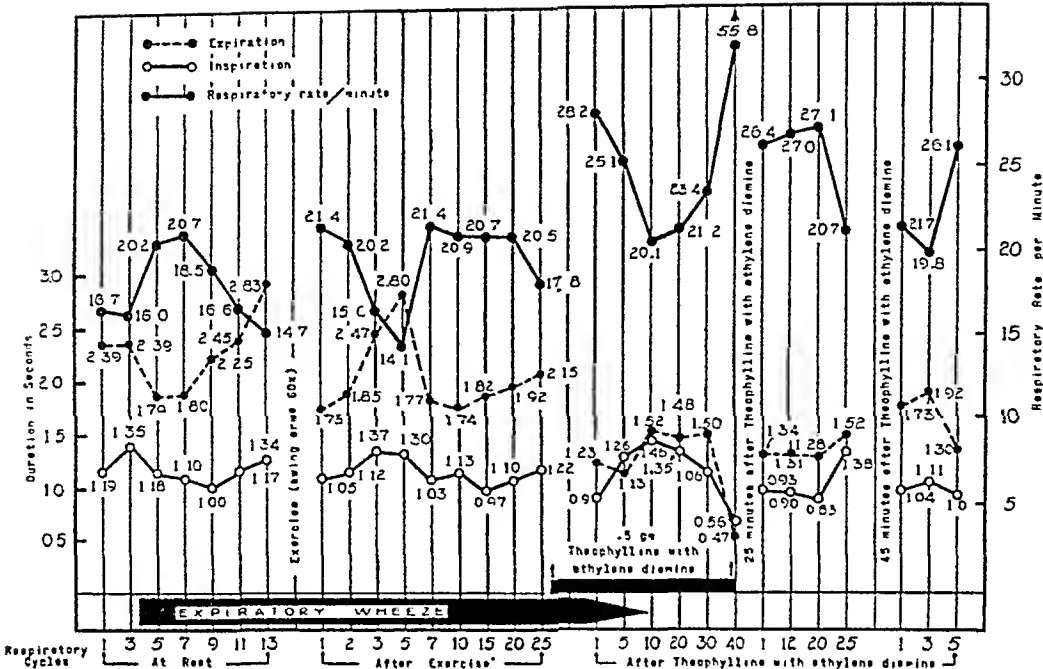


Fig. 4A.—Actual duration of expiration and inspiration (in seconds) per breath in patient with heart disease at rest, after exercise and after administration of aminophylline (Patient C. M.)

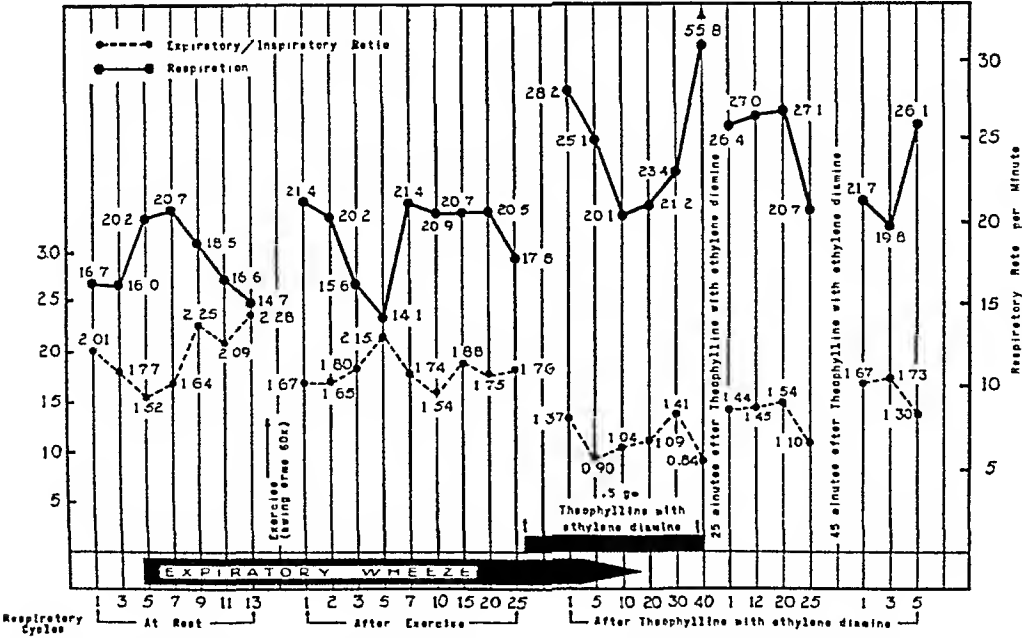


Fig. 4B.—Expiratory/inspiratory ratio for individual breaths in patient with heart disease at rest, after exercise, and after administration of aminophylline (same patient as in Fig. 4A).

Patients With Cardiac Dyspnea: Studies After Exercise.—After an amount of exercise which was capable of producing a perceptible hyperpnea in patients with heart disease, the same type of observations were made. Reference to Figs. 4A and 4B reveals that, although there was an increase in respiratory rate after exercise and a slight shortening of inspiration and expiration, this shortening was proportionately the same for both phases of each respiratory cycle. The selective shortening of expiration which was seen in normal subjects did not occur in the patient with dyspnea, or occurred to a much less pronounced degree. Careful observation of the patients with heart disease also revealed that after exercise the accessory muscles of both expiration and inspiration were utilized to a much greater degree than in normal subjects. Likewise, the expiratory:inspiratory ratio remained at about the resting level, or decreased only slightly in this group, as shown in Fig. 2. These findings were interpreted to indicate that under ordinary conditions the cardiac patients were not capable of the selective shortening of the expiratory phase which was exhibited in normal subjects.

Patients With Asthma.—Two subjects with allergic bronchial asthma who revealed prolonged wheezing expiration on auscultation were studied, and in each case there was found to be a marked prolongation of the expiratory phase, with a marked upward convexity of the expiratory limb (Fig. 1, B). The average expiratory:inspiratory ratio for these two patients at rest was found to be 2.14. Since these subjects were presumed to have had active bronchospasm, this was confirmatory proof of the presence of obstructive expiratory dyspnea. After an amount of exercise (forward bending to touch toes) capable of producing marked dyspnea, the average expiratory:inspiratory ratio was found to be 1.81. There was thus a slight shortening of the expiratory phase, but definitely not to the same degree as in the normal subjects. After the administration of 0.5 Gm. of aminophylline, intravenously, the expiratory:inspiratory ratio revealed an average value for the two subjects of 1.67, and measurements revealed a definite shortening of the expiratory phase. Furthermore, determinations of vital capacity in the patients with asthma revealed abrupt increases of considerable magnitude (Fig. 5) immediately after the drug. It was observed that expiration occurred with much greater ease after this medication was administered.

Patients With Cardiac Dyspnea After Administration of Aminophylline.—Figs. 4A and 4B reveal that after the administration of aminophylline there was a marked relative shortening of the expiratory phase. Examination of the tracings obtained during the administration of this drug also revealed a marked change in contour (Fig. 1, D and E) with a sharp and rapid expiration. In the majority of cases, the decrease in duration of expiration began within a few seconds after the intravenous injection of the drug was started. Six patients with heart disease were given aminophylline. Five patients showed a selective shortening of the expiratory phase with an average expiratory: inspiratory ratio of 1.46 during the intravenous administration of the drug. In comparison with the normal group (Fig. 2) it will be noted that this approaches the value for the same ratio determined after exercise in normal subjects. In each case there was a precipitous rise in the respiratory rate after the drug, which was considered to be of central

origin. This selective shortening of expiration which occurred after the administration of aminophylline was the more remarkable in that acceleration of the respiratory rate after exercise in patients with heart disease had failed to produce such a relative shortening. The vital capacity was measured before and immediately after the administration of aminophylline in five of the patients with cardiac dyspnea. Reference to Fig. 5 reveals that whereas in a normal subject the increase in vital capacity was insignificant, there was a definite increase in vital capacity (ranging from 150 to 800 c.c.) in the patients with heart disease (Table II). Since these increases occurred within periods of four to six minutes after

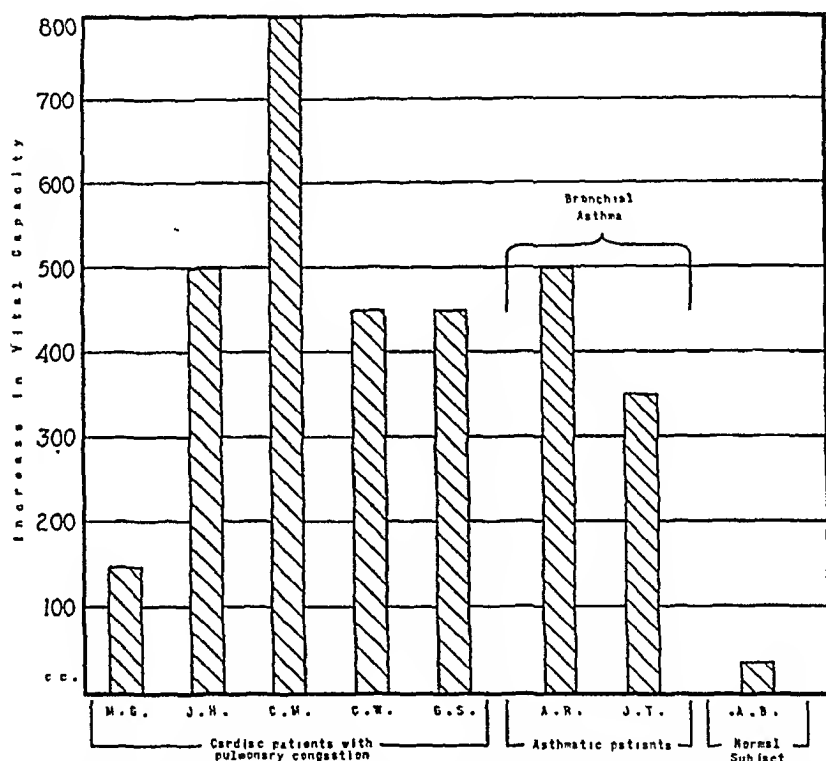


Fig. 5.—Increases in vital capacity after administration of aminophylline, 0.5 Gm. intravenously, in patients with heart disease, patients with bronchial asthma, and in a normal subject.

the beginning of the administration of the drug, and since moist râles were still present on auscultation and x-ray films of the chest showed the persistence of pulmonary congestion, the conclusion that there had been partial or complete abolition of variable degrees of bronchospasm seemed warranted. This was further supported by the fact that on auscultation of the chest of two of these patients who suffered from cardiac asthma, there was a prompt disappearance of expiratory, wheezing râles during the injection. Reference to Fig. 2 reveals that in the sixth subject, who suffered from very extreme pulmonary congestion, there was no alteration in the duration of expiration and the expiratory:inspiratory ratio after aminophylline. This was interpreted as indicating either that a severe degree of bronchospasm which was not relieved by the drug was present or that extreme pulmonary congestion had produced a leathery consistency of the lung with loss of normal elastic contractility.

TABLE II. VITAL CAPACITIES—PATIENTS WITH HEART DISEASE

PATIENT	AT REST (C.C.)	PREDICTED NORMAL (%)	AFTER AMINOPHYLLINE (C.C.)	INCREASE (C.C.)
1 (J. H.).....	2,200	48	2,700	500
2 (C. M.).....	2,600	79	3,400	800
3 (M. S.).....	2,200	50	2,650	450
4 (C. W.).....	1,900	43	2,350	450
5 (M. G.).....	2,100	49	2,250	150

DISCUSSION

The normal subjects were capable of a marked increase in respiratory rate and depth after exercise without severe subjective symptoms of dyspnea. This increase in rate was accomplished mainly by a selective shortening of the duration of expiration. These changes occurred with ease, to meet the needs for increased ventilation, and there was no apparent obstruction in either inspiration or expiration. Further, in a normal subject given aminophylline intravenously, there was only an insignificant increase in vital capacity.

In patients with cardiac dyspnea, the striking factors noted were a relative prolongation of the expiratory phase at rest, and a failure of this phase to undergo relative shortening after exercise. This prolongation of the expiratory phase was most strikingly seen in patients suffering from "cardiac" asthma, in whom the expiratory distress was easily found on auscultation, as evidenced by a prolonged, wheezing type of expiration. The pneumographic tracings obtained in both the patients with allergic asthma and those with cardiac asthma gave patterns which were almost identical in appearance. In each case the expiratory phase was markedly prolonged and was seen to possess an upward convexity. Patients with allergic asthma have previously been shown to have a definite prolongation of the expiratory phase by measurement of spirographic tracings.² Although the remaining seven cardiac patients with pulmonary congestion did not show prolonged, wheezing expiration on physical examination, careful measurements of their pneumographic tracings did reveal a relative prolongation of the expiratory phase well above its relative duration as determined in the normal subjects. The shape of the expiratory tracing in this latter group was intermediate between the configurations obtained in the normal subject and those with cardiac asthma but was also characterized by a tendency toward upward convexity.

After the administration of aminophylline, there was a prompt shortening of the relative duration of the expiratory phase in patients with cardiac dyspnea and with allergic asthma. This was accompanied by a significant increase in the vital capacity of both groups. Such increases in vital capacity in allergic asthma after the administration of aminophylline were observed in 1937 by Greene, Paul, and Feller,³ but data showing such increases do not appear to have been presented for patients with cardiac dyspnea, despite the wide usage of aminophylline in this condition.

Although the prolonged, wheezing expiration of cardiac asthma has long been recognized clinically, pneumographic tracings to confirm this prolongation of expiration have been lacking. Since both the cardiac patients with asthma and those without the asthmatic wheeze revealed a prolongation of the expiratory phase, and since both groups revealed a prompt decrease in relative duration of expiration after aminophylline, accompanied by a prompt rise in vital capacity, the assumption that bronchospasm was present in both groups seems justified. Since none of the patients with heart disease had any previous personal history of allergic manifestations, it seemed unlikely that the expiratory difficulty was due to allergy. The bronchospastic element observed probably has its origin from reflexes arising in the congested pulmonary tissues. This aspect of the problem needs further investigation.

SUMMARY

1. Pneumographic tracings of respiration revealed a similar type of distortion and prolongation of the expiratory phase in cardiac patients with pulmonary congestion and in patients with allergic asthma. Expiration in these patients did not undergo the relative shortening after exercise seen in normal subjects.

2. During the administration of aminophylline intravenously, the expiratory phase of the patients with heart disease and asthma shortened promptly. Determinations of vital capacity in both groups also revealed abrupt increases of considerable magnitude immediately after this drug.

3. The possibility that the changes observed in the patients with heart disease are due to reflex bronchospasm caused by pulmonary congestion is suggested.

The author wishes to express his gratitude to Dr. Tinsley R. Harrison for his suggestions and advice throughout this study.

REFERENCES

1. Caughey, J. L., Jr.: Analysis of Breathing Pattern, *Am. Rev. Tuberc.* **48**: 332, 1943.
2. Mudd, S. G.: Clinical Spirography. I. Observations in Bronchial Asthma, *Boston M. & S. J.* **193**: 345, 1925.
3. Greene, J. A., Paul, W. D., and Feller, A. E.: The Action of Theophylline With Ethylenediamine on Intrathecal and Venous Pressures in Cardiac Failure and on Bronchial Obstruction in Cardiac Failure and in Bronchial Asthma, *J. A. M. A.* **109**: 1712, 1937.
4. Silverman, L., Lee, R. C., and Drinker, C. K.: A New Method for Studying Breathing, with Observations Upon Normal and Abnormal Subjects, *J. Clin. Investigation* **23**: 907, 1944.
5. Schmidt, C. F., and Harer, W. B.: The Action of Drugs on Respiration. I. The Morphine Series, *J. Exper. Med.* **37**: 47, 1923.
6. Gesell, R., and White, F.: Recruitment of Muscular Activity and the Central Neurone After Discharge of Hyperpnea, *Am. J. Physiol.* **122**: 54, 1938.
7. Weiss, S., and Robb, G. P.: Cardiac Asthma (Paroxysmal Cardiac Dyspnea) and the Syndrome of Left Ventricular Failure, *J. A. M. A.* **100**: 1841, 1933.
8. Vaughan, W. T., Perkins, R. M., and Derbes, V. J.: Epinephrine and Ephedrine Analogues and Their Clinical Assay. *J. Lab. & Clin. Med.* **28**: 255, 1942.
9. Adrian, E. D.: Afferent Impulses in the Vagus and Their Effect on Respiration, *J. Physiol.* **79**: 332, 1933.
10. Peabody, F. W., and Wentworth, J. A.: Clinical Studies of the Respiration. IV. The Vital Capacity of the Lungs and Its Relation to Dyspnea, *Arch. Int. Med.* **20**: 443, 1917.

11. Binger, C. A. L.: The Lung Volume in Heart Disease, *J. Exper. Med.* 38: 445, 1923.
12. Harrison, T. R., Calhoun, J. A., and Harrison, W. G., Jr.: Congestive Heart Failure. XXI. Observations Concerning the Mechanism of Cardiac Asthma, *Arch. Int. Med.* 53: 911, 1934.
13. Steffensen, E. H., Brookhart, J. M., and Gesell, R.: Proprioceptive Respiratory Reflexes of the Vagus Nerve, *Am. J. Physiol.* 119: 517, 1937.
14. Gesell, R., Steffensen, E. H., and Brookhart, J. M.: The Interaction of the Rate and Depth Components of Respiratory Control, *Am. J. Physiol.* 120: 105, 1937.
15. Adrian, E. D., and Bronk, D. W.: The Discharge of Impulses in Motor Nerve Fibers. I. Impulses in Single Fibers of the Phrenic Nerve, *J. Physiol.* 66: 81, 1928.
16. Cournand, A., Brock, H. J., Rappaport, I., and Richards, D. W.: Disturbance of Action of Respiratory Muscles As a Contributing Cause of Dyspnea, *Arch. Int. Med.* 57: 1008, 1936.
17. Burwell, S. C.: The Pathological Physiology of Early Manifestations of Left Ventricular Failure, *Ann. Int. Med.* 16: 105, 1942.
18. Herrmann, G., Agnesworth, M. B., and Martin, J.: Successful Treatment of Persistent Extreme Dyspnea "Status Asthmaticus"—Use of Theophylline Ethylenediamine (Aminophylline, U. S. P.) Intravenously, *J. Lab. & Clin. Med.* 23: 135, 1937.

THE INFLUENCE OF AGE ON BLOOD PRESSURE

A STUDY OF 5,331 WHITE MALE SUBJECTS

HENRY I. RUSSEK, M.D., AND MAURICE M. RATH, PH.D., M.D., STATEN ISLAND,
N. Y., BURTON L. ZOHMAN, M.D., BROOKLYN, N. Y., AND
ISIDORE MILLER, M.D., NEW YORK, N. Y.

THE question as to whether or not a physiologic rise in normal blood pressure occurs with advancing age has not thus far been satisfactorily answered. Conflicting clinical and statistical interpretations moreover have led to a wide divergence of authoritative opinion as to what constitutes the upper limit of normal at different ages.

Within recent years the highest acceptable level of the systolic reading has been persistently lowered so that "100 plus the age" no longer finds favor even with those who employ the most liberal criteria for this physiologic measurement. In the last fifteen years many authorities¹⁻⁵ have designated 140 mm. Hg as the ceiling level for normal systolic blood pressure irrespective of age. According to this view,³ a systolic reading above 140 mm. "is just as abnormal in an old man as in a young one." On the other hand, it has been shown repeatedly that a relatively high percentage of normal persons in middle life and old age manifest levels in excess of this limit.⁶⁻⁸ Indeed, one of us (H. I. R.)⁸ found that 64 per cent of a group of one thousand elderly seamen would have been considered to have abnormally high blood pressure by this delimitation. Furthermore, if the upper level of normal systolic blood pressure had been lowered to 120 mm. Hg, as advocated by Robinson and Brucer,⁹ only 13 per cent of this entire series would have qualified as normal. In distinct contrast with these findings in older male groups have been the observations of blood pressure levels in young male adults. Thus, various reports¹⁰⁻¹² indicate that only 1 to 3 per cent of Army examinees in World War II had systolic blood pressures in excess of 150.

White¹³ has stated that under the excitement of the examination, 160 mm. might be acceptable as the upper limit of the systolic blood pressure, but he would not raise the diastolic level much, if any, above 90 millimeters. Nevertheless, a recent publication by White and associates¹⁴ suggests that even transient elevation of the systolic blood pressure above 150 is significant as a forerunner of sustained hypertension. The same conclusion was reached in regard to diastolic levels above 90. The follow-up studies of Hines,¹⁵ however, are not in accord with this view. This author noted that "in the group of patients who had systolic blood pressure of more than 140 mm. but diastolic blood pressure of less than

From the Cardiovascular Research Division, U. S. Marine Hospital, Staten Island, N. Y.
Published with permission of the Surgeon General, U. S. Public Health Service,
Received for publication Dec. 26, 1945.

85 mm., none had subsequent hypertension." It appeared to Hines that a diastolic reading of 85 mm. represents a critical level with respect to future hypertensive disease. The prognostic significance of transient elevation of the systolic blood pressure, therefore, does not yet seem clearly established.

In an endeavor to investigate further the relationship between age and blood pressure, we have studied an unselected group of merchant seamen, coastguardsmen, and civilian male subjects.

MATERIAL FOR STUDY

The blood pressure levels of 5331 white men between the ages of 40 and 95 years were analyzed. These subjects were observed at the U. S. Marine Hospital, Staten Island, the U. S. Public Health Service Dispensary, Washington, D. C., Sailors Snug Harbor, Staten Island, and the New York City Farm Colony, Staten Island. The latter two institutions were the source of most of the aged individuals. The subjects from the Marine Hospital were healthy merchant seamen and coastguardsmen chiefly in the fifth and sixth decades of life. The subjects from Sailors Snug Harbor were older, retired seamen in the seventh to tenth decades of life. An analysis of this group was previously reported by one of us (H.I. R.).⁸ The subjects from the U. S. Public Health Service Dispensary were candidates for civil service appointments, while those from the New York City Farm Colony were an older group of civilians, unemployed, indigent, or incapacitated by the infirmities of senescence. A study of the latter group has also been reported by one of us (I. M.).⁶ In all instances, two or more blood pressure readings were taken. In the younger subjects an attempt was made to minimize the effect of excitement by instituting a short period of rest between blood pressure readings and a friendly chat. The older subjects were accustomed to having their blood pressure measured during routine morning rounds. All of the subjects were ambulatory. The persons observed at the various institutions numbered as follows:

U. S. Marine Hospital	1,588
Sailors Snug Harbor	1,000
U. S. Public Health Service Dispensary	1,887
New York City Farm Colony	856
Total	5,331

RESULTS

Table I represents an analysis of average systolic and average diastolic blood pressure* by five- and ten-year intervals. It is observed that average systolic blood pressure and pulse pressure rise with advancing years. Average diastolic

*The level at the beginning of the fourth phase was taken as the diastolic blood pressure.

TABLE I. AVERAGE SYSTOLIC AND DIASTOLIC BLOOD PRESSURE OF MALE SUBJECTS 40 TO 95 YEARS OF AGE

AGE (YR.)	NUMBER OF CASES	AVERAGE SYSTOLIC BLOOD PRESSURE (MM. HG)	T*	AVERAGE DIASTOLIC BLOOD PRESSURE (MM. HG)	T	AVERAGE PULSE PRESSURE (MM. HG)
40 to 44	831	133.3 \pm 0.57†		84.8 \pm 0.37		48.5
45 to 49	809	137.0 \pm 0.68	4.0	86.6 \pm 0.36	1.0	50.4
50 to 54	767	138.9 \pm 0.82	1.8	87.0 \pm 0.42	0.6	51.9
55 to 59	647	142.4 \pm 1.02	2.6	87.7 \pm 0.57	1.0	54.7
60 to 64	566	147.7 \pm 1.16	3.4	87.6 \pm 0.60	0.0	60.1
65 to 69	558	154.2 \pm 1.22	4.1	88.5 \pm 0.67	0.9	65.7
70 to 74	402	155.1 \pm 1.37	1.6	87.0 \pm 0.72	1.4	68.1
75 to 79	370	160.6 \pm 1.31	2.6	88.2 \pm 0.88	1.1	72.4
80 to 84	255	160.4 \pm 1.65	0.0	86.8 \pm 0.95	1.1	73.6
85 to 95	126	164.0 \pm 2.22	1.5	90.0 \pm 1.26	1.5	74.0
40 to 49	1,640	135.1 \pm 0.44		85.8 \pm 0.27		49.3
50 to 59	1,414	140.8 \pm 0.64	7.4	87.4 \pm 0.35	3.7	53.4
60 to 69	1,124	150.8 \pm 0.84	9.5	88.1 \pm 0.50	1.2	62.7
70 to 79	772	158.6 \pm 0.96	6.1	87.6 \pm 0.57	0.5	71.0
80 to 95	381	161.7 \pm 1.34	1.8	87.9 \pm 0.78	0.5	73.8
40 to 59	3,054	138.5 \pm 0.37		86.5 \pm 0.21		52.0
60 to 95	2,277	153.9 \pm 0.58	23.0	87.8 \pm 0.32	3.2	66.1
40 to 95	5,331	144.7 \pm 0.35		87.1 \pm 0.18		57.6

*T, employed in this and Tables II, III, and IV, represents the number of times greater the observed difference between an average or proportion of one age group and that of the preceding age group is than the standard error of that difference.

†These values are standard errors.

blood pressure, on the other hand, increases only slightly with age, the largest increment occurring between the fifth and sixth decades. These trends are shown in Figs. 1 and 2.

Table II was constructed by calculating the percentage of persons in each age group having "normal" blood pressure (149/95 or less), systolic hypertension (systolic, 150 mm. or over; diastolic, 95 mm. or less), and diastolic hypertension (diastolic, 96 mm. or over). A steady and progressive decrease in the incidence of "normal" blood pressure occurs with advance of age, the fall being from 87.2 per cent in the 40- to 44-year age group to 27.8 per cent in the 85- to 95-year age group. In direct contrast, a marked increase is noted in the frequency of systolic hypertension, the change being from 4.2 per cent to 45.2 per cent in the same age interval. When diastolic hypertension is analyzed, the incidence is found to rise from 9.6 per cent in the fifth decade to 20.2 per cent in the seventh decade, remaining relatively unchanged thereafter. Fig. 3 graphically represents the variations with age in the incidence of "normal" blood pressure, systolic hypertension, and diastolic hypertension.

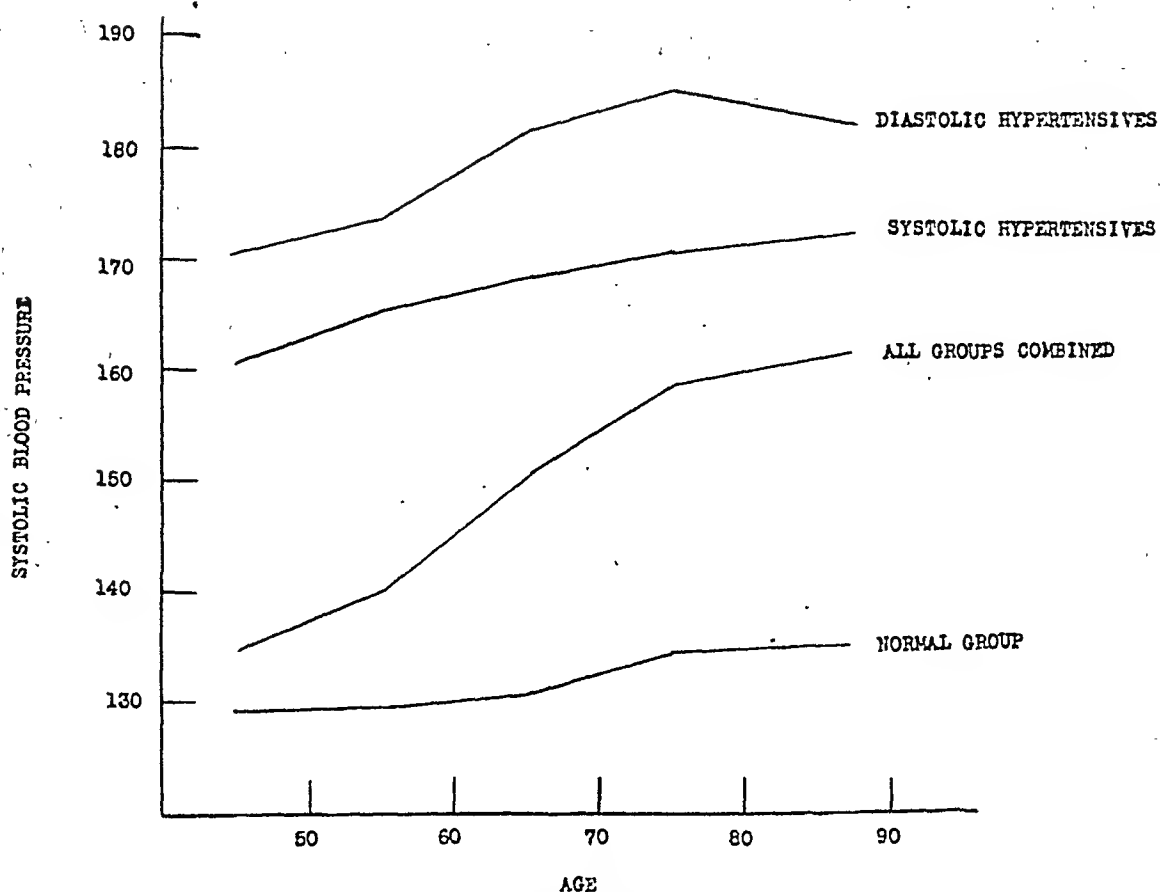


Fig. 1.—The relationship of age to average systolic blood pressure.

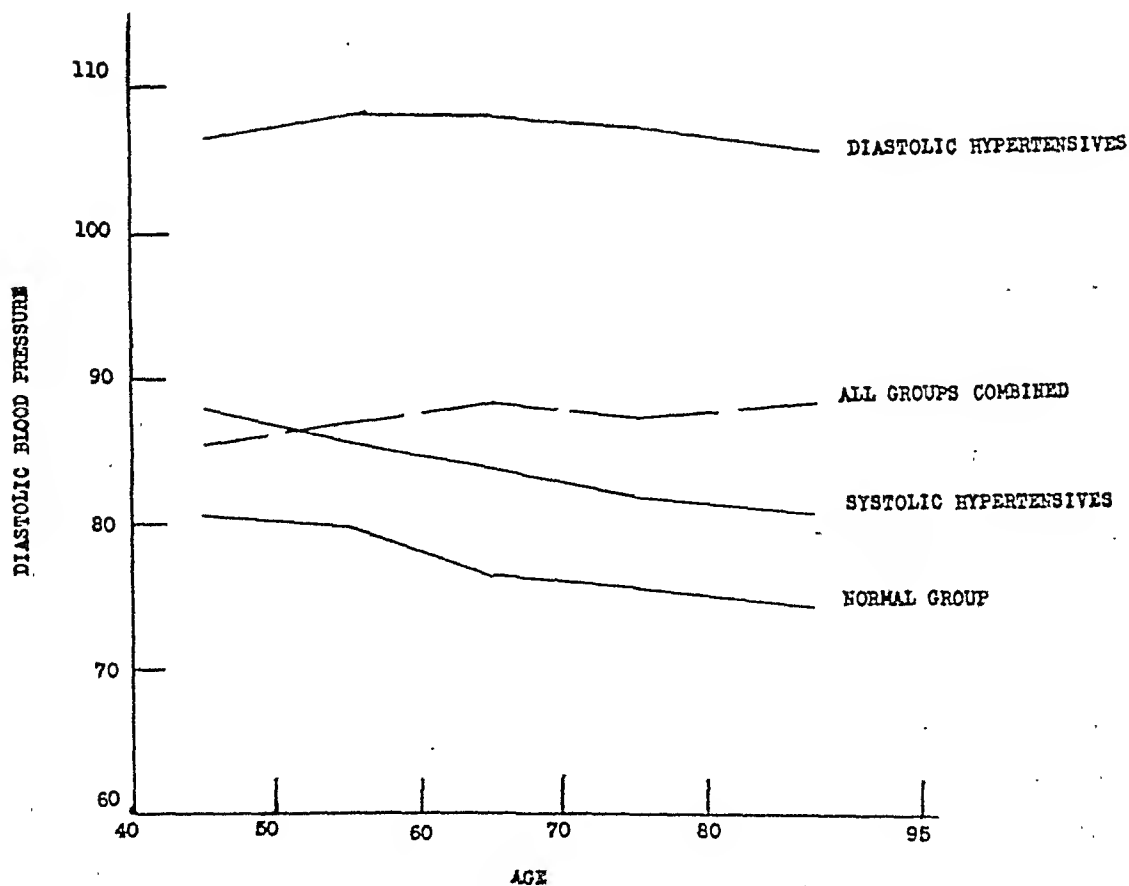


Fig. 2.—The relationship of age to average diastolic blood pressure.

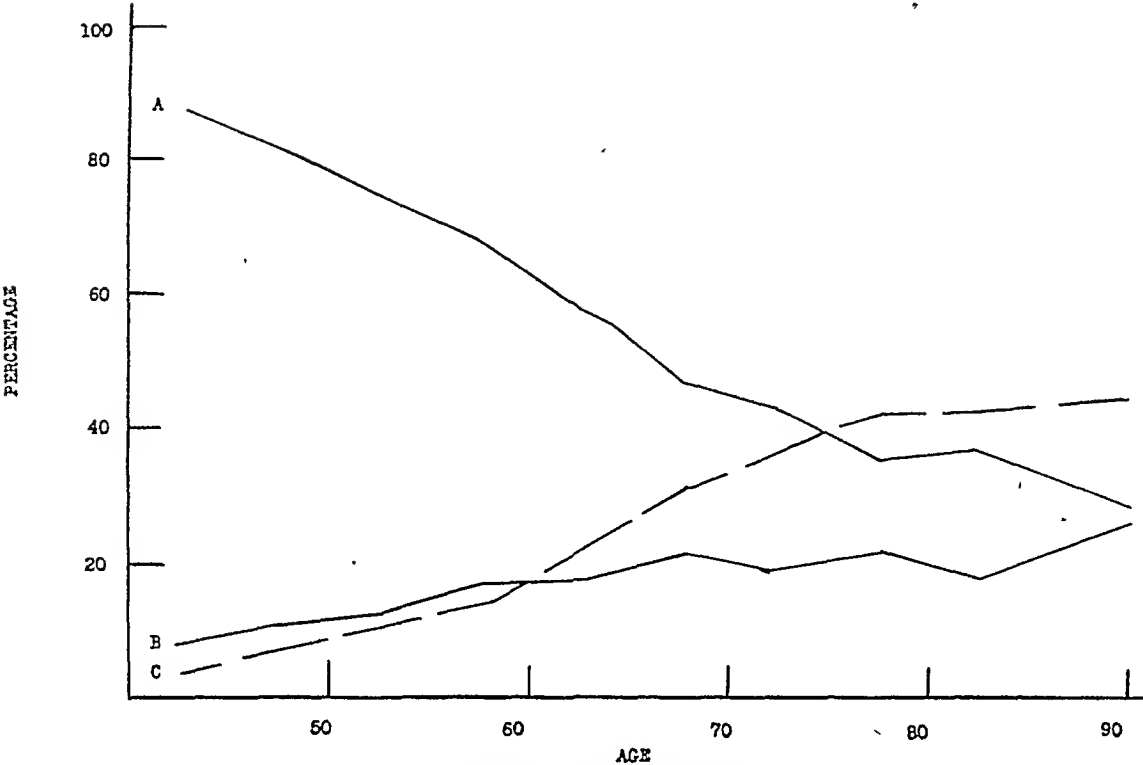


Fig. 3.—The relationship of age to percentage incidence of normal blood pressure (A), diastolic hypertension (B), and systolic hypertension (C).

TABLE II. PERCENTAGE INCIDENCE OF NORMAL BLOOD PRESSURE, SYSTOLIC HYPERTENSION, AND DIASTOLIC HYPERTENSION

AGE (YR.)	NORMAL BLOOD PRESSURE		SYSTOLIC HYPERTENSION		DIASTOLIC HYPERTENSION	
	%	T	%	T	%	T
40 to 44	87.2		4.2		8.5	
45 to 49	81.7	3.1	7.5	2.9	10.8	1.5
50 to 54	74.8	3.3	11.5	2.6	13.7	1.8
55 to 59	68.2	2.7	14.7	1.8	17.1	1.8
60 to 64	57.9	3.7	22.8	3.6	19.3	0.9
65 to 69	47.8	3.4	31.0	3.1	21.1	0.8
70 to 74	43.0	1.4	38.3	2.3	18.7	1.0
75 to 79	35.1	2.2	43.0	1.3	21.9	1.1
80 to 84	36.1	0.2	44.3	0.1	19.6	0.8
85 to 95	27.8	1.6	45.2	0.1	27.0	1.6
40 to 49	84.5		5.8		9.6	
50 to 59	71.8	8.4	12.9	6.7	15.3	4.7
60 to 69	52.9	9.9	26.9	8.7	20.2	3.2
70 to 79	39.2	6.0	40.5	6.1	20.2	0.0
80 to 95	33.3	2.0	44.6	3.6	22.0	0.7
40 to 59	78.6		9.1		12.3	
60 to 95	45.0	18.6	34.4	10.5	20.6	3.2
40 to 95	64.3		20.0		15.8	

TABLE III. "NORMAL" BLOOD PRESSURE GROUP

AGE (YR.)	NUMBER OF CASES	SYSTOLIC BLOOD PRESSURE		DIASTOLIC BLOOD PRESSURE		PULSE PRESSURE AVERAGE (MM.)
		AVERAGE (MM.)	T	AVERAGE (MM.)	T	
40 to 49	1,386	129.6 \pm 0.28		80.9 \pm 0.20		48.7
50 to 59	1,015	129.6 \pm 0.38	0.0	80.1 \pm 0.26	2.5	49.5
60 to 69	595	130.2 \pm 0.55	0.9	76.8 \pm 0.39	7.4	53.4
70 to 79	303	133.7 \pm 0.87	3.4	75.7 \pm 0.60	1.5	58.0
80 to 95	127	134.1 \pm 1.0	0.3	74.5 \pm 0.93	1.0	59.6
40 to 59	2,401	129.6 \pm 0.24		80.6 \pm 0.16		49.0
60 to 95	1,025	131.7 \pm 0.40	4.5	76.2 \pm 0.30	13.3	55.5
40 to 95	3,426	130.3 \pm 0.20		79.2 \pm 0.15		51.1

AGE (YR.)	SYSTOLIC BLOOD PRESSURE		DIASTOLIC BLOOD PRESSURE				120/80 OR LESS	
	140-149 MM.		90-95 MM.		BELOW 70 MM.			
	%	T	%	T	%	T	%	T
40 to 49	18.6		15.4		3.6		27.5	
50 to 59	24.4	2.0	14.4	0.7	6.4	3.0	29.0	0.8
60 to 69	28.2	3.0	12.2	1.3	15.1	5.2	32.1	1.3
70 to 79	36.3	2.4	15.1	1.5	20.1	1.7	26.0	1.9
80 to 95	40.9	0.9	15.7	0.2	21.2	0.3	26.7	0.0
40 to 59	19.8		15.0		4.7		28.1	
60 to 95	32.1	7.2	13.5	1.1	16.5	9.5	29.7	1.1
40 to 95	23.5		14.6		8.5		28.6	

The trends of "normal" systolic and "normal" diastolic blood pressure are analyzed with respect to age in Table III. Average "normal" systolic pressure tends to increase progressively from 129.6 mm. in the 40- to 49-year age group to 134.1 mm. in the 80- to 95-year age group. Comparison of average "normal" systolic pressure in the age period 40 to 59 with that in the age period 60 to 95 shows a significantly higher level in the older group. Average "normal" diastolic pressure tends to decrease progressively from 80.9 mm. in the 40- to 49-year age group to 74.5 mm. in the 80- to 95-year age group. The incidence of blood pressures of 120/80 or less shows no significant change with advancing years. In sharp contrast, one observes a significant rise with age in the frequency of systolic blood pressures between 140 and 149 millimeters. There is also an increasing incidence of diastolic blood pressures below 70. The frequency of diastolic pressures over 90 mm., on the other hand, is not altered in the "normal" group with succeeding decades. It appears, therefore, that the trend of normal systolic blood pressure with age is upward, while that of normal diastolic blood pressure is downward. If the rise in "normal" systolic pressure were due solely

TABLE IV. AVERAGE SYSTOLIC AND DIASTOLIC BLOOD PRESSURE OF MALE SUBJECTS WITH SYSTOLIC AND DIASTOLIC HYPERTENSION

AGE (YR.)	AVERAGE SYSTOLIC BLOOD PRESSURE				AVERAGE DIASTOLIC BLOOD PRESSURE			
	SYSTOLIC HYPERTENSION		DIASTOLIC HYPERTENSION		SYSTOLIC HYPERTENSION		DIASTOLIC HYPERTENSION	
	MM. HG	T*	MM. HG	T†	MM. HG	T*	MM. HG	T*
40 to 49	160.8		168.4		87.7		106.9	
50 to 59	164.8		175.9		85.9		108.5	
60 to 69	168.0		182.1		83.7		107.9	
70 to 79	168.9		186.8		81.9		107.3	
80 to 95	171.9		182.5		81.5		105.6	
40 to 59	163.4 ± 0.78		171.9 ± 1.27	5	86.6 ± 0.60		107.8 ± 0.52	
60 to 95	169.1 ± 0.53	6.4	184.7 ± 1.13	10	82.5 ± 0.35	7.6	107.3 ± 0.44	5.6
40 to 95	167.6 ± 0.44		179.7 ± 0.89	12	83.6 ± 0.39		107.5 ± 0.38	0.7

*Refers to values between 40- 50-year age group and 60- 95-year age group.

†Refers to values comparing subjects with systolic hypertension with those with diastolic hypertension within the same age group.

to potential hypertension in the "normal" group, an associated rise in "normal" diastolic pressure should be demonstrable. This, however, is not found. On the contrary, average "normal" diastolic pressure actually falls with age and there is, correspondingly, a progressive increase in the percentage of subjects with low levels of normal.

Our studies indicate that the average systolic blood pressure of each of the groups, "normal," systolic hypertensive, and diastolic hypertensive, increases significantly with advance of age. With respect to diastolic blood pressure, the averages for both "normals" and subjects with systolic hypertension decrease with age, while the average diastolic blood pressure for subjects with diastolic hypertension remains unchanged (Tables III and IV). Since in none of these individual blood pressure groups does the average diastolic pressure rise with age, the question may be raised as to why it shows this tendency when the entire group is considered as a whole. The answer undoubtedly lies in the rising incidence of diastolic hypertension with advancing age, a factor tending to elevate the average pressure of the combined groups. The trends in average systolic and average diastolic blood pressure for each of the blood pressure groups as well as for the total series is shown in Figs. 1 and 2, respectively.

DISCUSSION

Increase in average blood pressure with age does not constitute proof of a physiologic rise in normal blood pressure, for it is obvious that the hypertensive levels in the total population may distort the true picture of normal blood pressure trends. Robinson and Brucer, using 140/90 as the upper limit of normal, reported no increase in the mean arterial blood pressure with advancing years and thus concluded that normal blood pressure remains constant throughout life. Our examination of their data, however, does not uphold this view, for we discovered a significant rise with age in the incidence of systolic blood pressures in their upper range of "normal" (130 to 139 mm.). Furthermore, although these authors contended that the conclusions from their analysis would have been the same if the level of delimitation had been placed at 150 systolic and 95 diastolic, we have found, employing these ceiling values for normal in our series, that there is a tendency for normal systolic blood pressure to rise with advance of age (Table III). Moreover, if this increase were due chiefly to the presence of potential or latent hypertension in the "normal" group as alleged by these authors, a concomitant rise in diastolic blood pressure would also have been evident. Actually, however, a decrease rather than increase in "normal" diastolic pressure is observed with advance of age. We noted that the frequency of upper levels of "normal" diastolic blood pressure (90 to 95 mm.) remains unchanged when successively older groups are analyzed. On the other hand, the percentage of persons with systolic pressures in the upper range of "normal" (140 to 149 mm.), as well as the percentage with diastolic pressures in the lower range of normal (below 70 mm.), increase appreciably. Robinson and Brucer similarly found a rising incidence of low diastolic levels after the age of 55 years but admitted

that they "have not adequately accounted for this variation." The findings strongly suggest, therefore, that age exerts a definite influence on normal blood pressure, the systolic level rising and the diastolic level falling with advancing years. Why normal blood pressure is affected in this manner will now be considered.

Observations of various workers indicate that the physiologic process of aging influences all blood pressure levels through two major mechanisms, one neurogenic the other vascular. Russek¹⁶ and Russek and Zohman,¹⁷ using the cold-pressor test, have demonstrated that the reactivity of the blood pressure increases progressively as persons grow older. This increase in vasopressor response is attributed by Raab¹⁸ to "increasing irritability of the cerebromedullary vasoconstrictor centers" with advancing years. The latter allegedly results from ischemia of the nerve centers controlling vascular tonus, a consequence of diminution in cerebral blood flow due to arteriolar sclerotic changes. That hypertension may actually arise from decreased cerebral blood flow is suggested by the recent experiments of Fishback and co-workers,¹⁹ who were able to produce sustained elevation of the blood pressure in animals by ligating the arteries supplying the head. On the other hand, Dock²⁰ rejects the explanation that cerebral arteriosclerosis is responsible for increased vasomotor irritability and hypertension, declaring that these are rather the result of deterioration of the central nervous system with trophic loss of neurones associated with aging. Thus, vascular hyperreactibility and benign hypertension, in the opinion of Dock, are similar in origin to "senile intention tremor, Parkinsonism, and other involutional disorders of specific neurone groups." Whatever the explanation, evidence suggests that systolic and diastolic blood pressures are increasingly prone to transient elevation with advancing years. Although it has been maintained that a hyperreactive vascular system portends future hypertension, Russek and Zohman¹⁷ found an increasing frequency of hyperreaction with age in subjects "unlikely to develop the disease" and even in those with hypotension. It seems possible, therefore, that other factors in addition to neurogenic vascular hyperreactibility are essential for the development of sustained hypertension. Sensitization of the vascular system by hormones from the adrenal cortex, adrenalin, angiotonin, or other substances, may be a necessary accompaniment. That a neurogenic mechanism is of importance in the pathogenesis of hypertension is reflected in the ability of caudal anesthesia^{21,22} and lumbodorsal splanchnicectomy²³ to reduce hypertensive levels to normal in many cases. The neurogenic factor, therefore, appears to exert an influence tending to augment both systolic and diastolic blood pressure with advance of age.

A second mechanism, of purely vascular origin, also alters the blood pressure as one grows older. Diminution in the elasticity of the aorta and its large branches due to arteriosclerosis has been held responsible for the appearance of systolic hypertension in older groups. However, Herringham and Wills²⁴ and others have shown that the elasticity of arteries diminishes progressively with advancing years, becoming particularly marked with the fifth decade. Although loss of elasticity is frequently accepted as synonymous with ather-

osclerosis, it has been emphasized that many elderly persons have vessels with little elasticity remaining but no atherosclerosis. Contrariwise, extensive sclerotic changes may be present even in young persons without significant loss of elasticity.²⁵ Normal vascular aging, therefore, appears to be reflected in a rising systolic pressure and falling diastolic pressure with advancing years. Systolic hypertension in the aged is undoubtedly a manifestation of the same vascular process. Considered in this light, these changes may be compared to the physiologic alterations occurring in the hair, skin, skeleton, and other structures with advancing years.

These considerations make it apparent that the neurogenic and vascular factors are summated in their influence upon systolic blood pressure while exerting opposing influences upon diastolic blood pressure. In normal persons and in those with systolic hypertension the vascular factor appears to dominate, as shown by a tendency of the average diastolic blood pressure to fall with age in each of the two groups. This change, however, is not observed in the group with diastolic hypertension.

Although only 9.1 per cent of the persons between 40 and 59 years had systolic hypertension, 34.4 per cent of the persons between 60 and 95 years manifested this type of blood pressure elevation. If it be accepted, therefore, that systolic blood pressure increases with age and that systolic hypertension is a normal finding in later life, the upper limit of normal systolic pressure for older groups must be elevated considerably above present-day standards. Indeed, the old dictum "100 plus the age" may yet regain its former prestige as an index of normal systolic blood pressure.

Acceptance of 140 mm. as the ceiling level for normal systolic blood pressure as advocated by others would have eliminated almost one-half (49.3 per cent) of our entire series. For the subjects between the ages of 60 and 95 years, 69.1 per cent would have been excluded by this limit. Furthermore, only 18.3 per cent of the entire series would have qualified as normal under the standards set by Robinson and Brucer (120/80 or less). Although 69.1 per cent of the persons between 60 and 95 years had systolic pressures of 140 mm. and over, only 41.9 per cent had diastolic pressures of 90 mm. and over. Hence, if these readings are employed as limits of normal, it is evident that there is a wide disparity in the "screening" value of the respective levels.

Most authorities accept small increments in the diastolic blood pressure with age as physiologic. We have pointed out, however, the tendency of normal diastolic blood pressure to fall rather than rise with age. It seems likely from studies of younger groups that normal diastolic blood pressure rarely exceeds 90.¹³⁻¹⁵ If this is established, our observations would indicate that an even lower ceiling may be applicable to older age groups.

From these considerations it would appear that essential hypertension cannot be defined solely in terms of the systolic blood pressure, although this has been a common practice in earlier literature and even in some current literature. In general, our observations seem to support the views of Hines,¹⁵ who, in his follow-up studies, noted that the diastolic pressure alone and not the systolic is of value in prognosticating the subsequent development of hypertension.

SUMMARY AND CONCLUSIONS

Although previous studies of unselected groups have demonstrated a progressive rise in *average* systolic and diastolic blood pressure with advancing years, no convincing proof has been offered that *normal* blood pressure increases physiologically with respect to age. Considerable difference of opinion exists, therefore, as to what constitutes the limits of normal at various periods of life.

A statistical analysis of the blood pressure levels of 5,331 white male subjects between the ages of 40 and 95 years is presented. The variations in blood pressure with age and the inferences drawn therefrom are as follows:

1. *Average* systolic blood pressure increases significantly with age, whereas *average* diastolic blood pressure shows little variation after the sixth decade.

2. The incidence of "normal" blood pressure (149/95 or less) falls markedly with age so that less than one-half (45.0 per cent) of the subjects 60 years old and older belong to this group.

3. The frequency of systolic hypertension rises sharply with advancing years. Approximately one-third (34.4 per cent) of the subjects 60 years of age and over show this type of blood pressure elevation.

4. The incidence of diastolic hypertension increases significantly up to the seventh decade, remaining relatively unchanged thereafter.

5. *Normal* systolic blood pressure tends to increase with age. The frequency of upper levels of "normal" (140 to 149 mm.) rises appreciably with advancing years.

6. The assumption that *normal* diastolic blood pressure increases with age is unfounded. Actually, a progressive decrease occurs with succeeding decades with the result that there is an increasing frequency of low diastolic levels (below 70 mm.) with advancing years.

7. The rise in normal systolic pressure and concomitant fall in normal diastolic pressure are primarily the result of progressive diminution in the elasticity of the aorta and its large branches associated with the process of aging (vascular factor).

8. The same physiologic mechanism is responsible for the increasing incidence of systolic hypertension which is merely the hemodynamic reflection of vascular aging.

9. Physiologic changes in the central nervous system leading to vascular hyperreactibility with advancing years similarly exert an important influence upon the blood pressure trends of all groups (neurogenic factor).

10. Both mechanisms (vascular and neurogenic) are summated in their effect upon systolic blood pressure while exerting opposing influences upon diastolic blood pressure.

11. The old maxim "100 plus the age" may actually be a fair index of normal systolic blood pressure.

12. Although the ceiling for normal diastolic blood pressure has been set at 90 mm. Hg, an even lower level appears applicable after middle age.

13. Essential hypertension cannot be defined solely in terms of the systolic blood pressure. It is the diastolic level alone that determines the existence of this disease.

REFERENCES

1. Stieglitz, E. J.: Abnormal Arterial Tension, New York, 1935, National Medical Book Company.
2. Allen, E. V., in Musser, J. H.: Internal Medicine, ed. 3, Philadelphia, 1938, Lea & Febiger.
3. Alvarez, W. C., and Stanley, L. I.: Blood Pressure in Six Thousand Prisoners and Four Hundred Prison Guards: Statistical Analysis, Arch. Int. Med. 46: 17, 1930.
4. Huber, E. G.: Systolic and Diastolic Blood Pressure in Healthy Men, Human Biol. 5: 542, 1933.
5. Faught, F. A.: Simple Method for Determining Normal Average Systolic Blood Pressure at Any Age, M. J. & Rec. 135: 160, 1932.
6. Miller, I.: Blood Pressure Studies in the Aged, New York State J. Med. 41: 1631, 1941.
7. Master, A. M., Marks, H. H., and Dack, S.: Hypertension in People Over Forty, J. A. M. A. 121: 1251, 1943.
8. Russek, H. I.: Blood Pressure in the Aged, AM. HEART J. 26: 11, 1943.
9. Robinson, S. C., and Brucer, M.: Range of Normal Blood Pressure; Statistical and Clinical Study of 11,383 Persons, Arch. Int. Med. 64: 409, 1939.
10. Folk, O. H., McGill, K. H., and Rowntree, L. G.: Analysis of Reports of Physical Examinations, M. Statist. Bull., Sel. Serv. Syst., No. 1, Nov. 10, 1941, Washington, D. C., National Headquarters, Selective Service System.
11. (a) Wilburne, M., and Ceccolini, E. M.: A Note on the Incidence of Arterial Hypertension in 25,000 Army Examinees, Army M. Bull. 68: 118, 1943.
(b) Wilburne, M., and Ceccolini, E. M.: Heart Disease in Selective Service Examinees; Study of 20,000 Examinees in Pacific Northwest, Am. J. M. Sc. 207: 204, 1944.
12. Flaxman, N.: Initial Cardiac Examination of 23,000 Inductees and Volunteers, Am. J. M. Sc. 209: 657, 1945.
13. White, P. D.: Cardiac Problems in War Time, Ann. Int. Med. 18: 323, 1943.
14. Levy, R. L., White, P. D., Stroud, W. S., and Hillman, C. C.: Transient Hypertension, the Relative Prognostic Importance of Various Systolic and Diastolic Levels, J. A. M. A. 128: 1059, 1945.
15. Hines, E. A., Jr.: Range of Normal Blood Pressure and Subsequent Development of Hypertension; Follow-up Study of 1,522 Patients, J. A. M. A. 115: 271, 1940.
16. Russek, H. I.: The Significance of Vascular Hyperreaction as Measured by the Cold-Pressor Test, AM. HEART J. 26: 398, 1943.
17. Russek, H. I., and Zohman, B. L.: Influence of Age Upon Blood Pressure Response to the Cold-Pressor Test, AM. HEART J. 29: 113, 1945.
18. Raab, W.: Hormonal, Central and Renal Origin of "Essential" Hypertension (Cerebral and Renal Arteriosclerotic Ischemia as Causal Factors), Ann. Int. Med. 14: 1981, 1941.
19. Fishback, H. R., Dutra, F. E., and MacCamy, E. T.: The Production of Chronic Hypertension in Dogs by Progressive Ligation of Arteries Supplying the Head, J. Lab. & Clin. Med. 28: 1187, 1943.
20. Dock, W.: Presbycardia, or Aging of the Myocardium, New York State J. of Med. 45: 983, 1945.
21. Russek, H. I., Southworth, J. L., and Zohman, B. L.: Continuous Caudal Anesthesia as a Test in the Selection of Hypertensive Patients for Sympathectomy, J. A. M. A. 128: 1225, 1945.
22. Russek, H. I., Southworth, J. L., and Zohman, B. L.: Selection of Hypertensive Patients for Sympathectomy, J. A. M. A. 130: 937, 1946.
23. Smithwick, R. H.: A Technic for Splanchnic Resection for Hypertension: Preliminary Report, Surgery 7: 1, 1940.
24. Herringham, W. P., and Wills, W. A.: On the Elasticity of the Aorta: Being a Contribution to the Study of Arterial Sclerosis, Trans. Med.-Chir. Soc. Edinburgh 69: 499, 1904.
25. Page, I. H.: Arteriosclerosis and Lipoid Metabolism In Ageing and Degenerative Diseases Biol. Symposia 11: 43, 1945.

THE T WAVE OF THE PRECORDIAL ELECTROCARDIOGRAM AT DIFFERENT AGE LEVELS

RAMON M. SUAREZ, M.D., AND RAMON M. SUAREZ, JR., M.D.

SAN-JUAN, PUERTO RICO

THIS paper is the first of a series dealing with the electrocardiographic study of 161 healthy Puerto Ricans. The subjects studied included 50 soldiers between 19 and 46 years of age; 31 women between the ages of 19 and 45 selected from the technical, nursing, and secretarial personnel of the University Hospital at San Juan, Puerto Rico; 20 young boys and 20 young girls ranging in age between 12 and 18 years; and 20 male and 20 female children between the ages of 5 and 11, most of them inmates of the Boys' and Girls' Charity Schools of our Insular Department of Health. All subjects were in an apparently normal state of health, with negative serologies, no histories of rheumatic arthritis, and no evidences of valvular heart lesion.

The standard leads were taken first in each case. Potential variations of the right arm (VR), the left arm (VL), the left leg (VF), and of the six precordial points were obtained by pairing an exploring electrode with a central terminal connected to the right arm, the left arm, and the left leg through a resistance of 5,000 ohms each. Wilson's central terminal with Goldberger's modification for augmented limb leads was used.

In taking the extremity and precordial leads, the connections of the galvanometer were so made that an upward deflection represented positivity of the exploring electrode and a downward deflection, negativity. The standard and extremity potentials were taken at normal sensitivity of the string (1 cm. = 1 mv.) and the precordial potentials at half normal sensitivity (1 cm. = 2 mv.). The six precordial points used were those specified by the Committee on Precordial Leads of the American and of the British Heart Association.¹ All tracings were made between 9 and 12 A. M. with the subjects in the reclining position.

We did not include older persons in our investigation, as the work of Willius,² Levitt,³ Taran and Kaye,⁴ Warnecke,⁵ and Gelman and Brown⁶ have proved conclusively that no less than 25 per cent of these subjects show distinct electrocardiographic abnormalities. Taran and Kaye, in their study of 102 men and women between 60 and 90 years of age, reported abnormal T waves in one-fourth of them. These findings were most commonly observed in the ninth decade and less often in the eighth, the most frequent finding being a negative T₄. Abnormal findings were as frequent in women as in men. The aged, therefore, cannot be considered normal individuals from a cardiovascular standpoint.

From the School of Tropical Medicine and the Mimlra Hospital.
Received for publication Jan. 25, 1946.

Electrocardiographic studies of young adults have been performed by several investigators. We shall mention here Shanno,⁷ who studied 100 student nurses of 18 to 22 years of age with the conventional leads and the precordial electrocardiograms CF_1 and CF_6 ; Larsen and Skúlason,⁸ who analyzed the extremity deviations from 50 men and 50 women; Deeds and Barnes,⁹ who studied

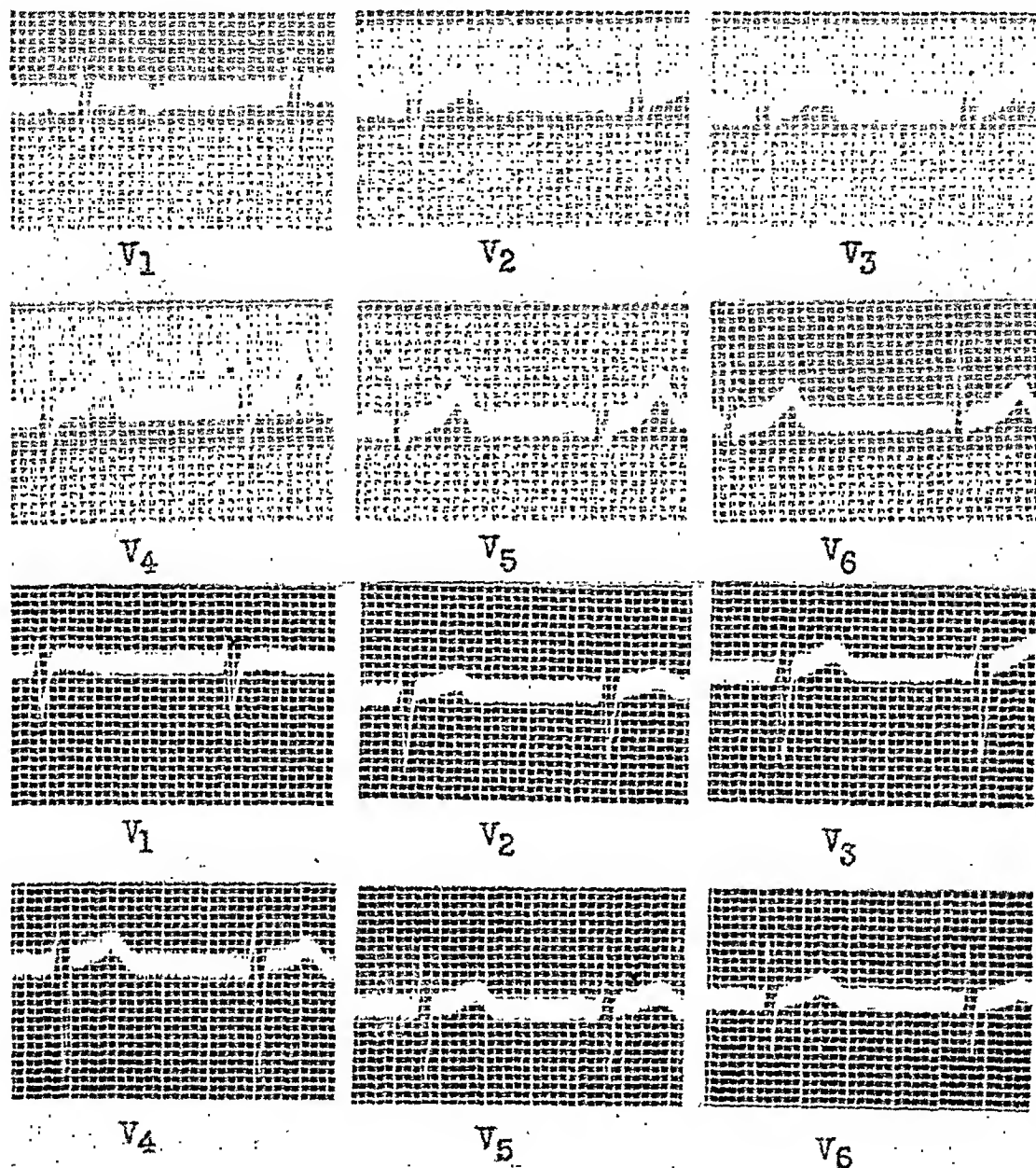


Fig. 1.—A, Case 776. P. R., aged 28 years, male. Negative T wave only in V_1 . B, Case 787. M. H., aged 28 years, male. Negative T wave only in V_1 . Both cases are typical of the electrocardiographic pattern of adult males.

the characteristics of the chest lead electrocardiograms of 100 normal adults and claim that CR is better than CL and CF. In one instance they found that the T wave approached negativity in Lead CF_2 , but this never occurred in CR_2 . Thomas¹⁰ concludes that "until the limits of normal variation in the human electrocardiogram have been much more thoroughly explored, the diagnosis of heart

disease in young persons should seldom be based on electrocardiographic findings alone, in the absence of clinical manifestations.” In an analysis of electrocardiograms obtained from 1,000 healthy aviators, Graybiel, McFarland, Gates, and Webster¹¹ utilized only the three standard leads and Lead IV F. In the latter they found that the T wave was upright in all but two instances, when it was

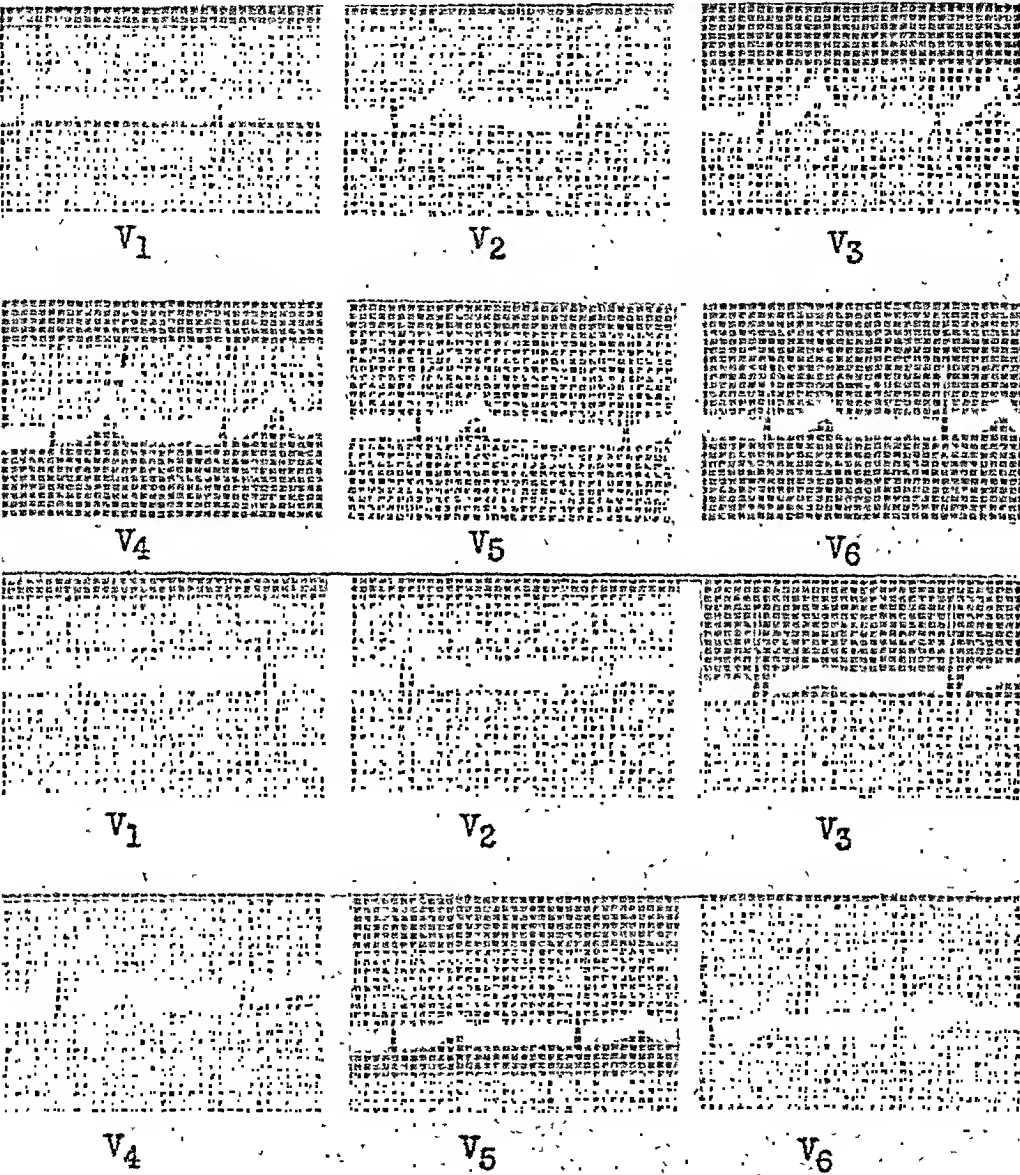


Fig. 2.—A, Case S12. A. Q., aged 28 years, female. No inverted T wave. B, Case S11. S. U., aged 19 years, female. Inverted T wave in V₁, diphasic in V₂.

diphasic. The range of the T wave was 1 to 15 mm. and the mean, 5.9 millimeter. Huge T waves, they state, are rarely observed in healthy persons. Kossman and Johnston¹² studied 30 subjects and published their table of normal values of the ventricular deflections for the standard and unipolar special leads.

Fetal electrocardiograms have rarely been taken with special apparatus,¹³ and electrocardiographic studies in children have not been numerous. Lepeschkin¹⁴ studied the normal chest electrocardiogram in 50 children from 2 weeks to 15 years of age. "The T wave," he says, "is inverted on the right chest anteriorly and upright on the left. On transition, a diphasic T is found. This transition is more to the left anteriorly in children than in grownups, and this deviation from the midline is greater the younger the child. These differences are related to the more lateral position of the interventricular groove in the younger child." Gelman and Brown⁶ reported the electrocardiograms of 121 normal children between 12 and 14 years of age and compared them with a group of "normals" over the age of 61. These authors used only the three conventional leads.

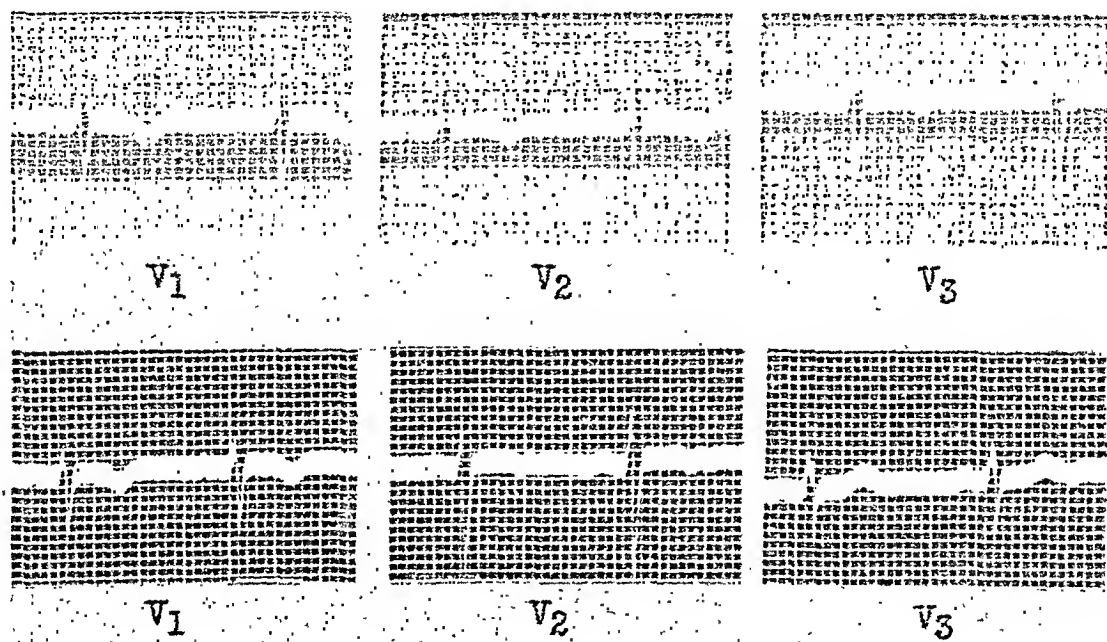


Fig. 3—Case 810. R. M. O., aged 20 years, female. Negative T wave in V_1 , V_2 , and V_3 (upper row). Same subject a few days later, using identical technique and approximately the same precordial points, showed negative T wave only in V_1 and V_2 (lower row). In both instances heart was in semi-vertical position. Axes of $+58^\circ$ in the first position and $+68^\circ$ in the second.

Master, Dack, and Jaffe¹⁵ studied the precordial leads in 71 normal children from 2 to 15 years of age. An upright or diphasic T wave to the left of the sternum, abnormal in adults, occurred in 60 per cent of the children. It was most frequent over the sternum, the incidence decreasing as the apex was approached, as in increasing age. No correlation was found between the shape of the heart or axis deviation and the presence of upright T waves. (The galvanometer connections were arranged so that upright deviations represented negative potentials.)

Groedel, Kisch, and Reichert¹⁶ and Groedel and Miller¹⁷ reported electrocardiographic studies in the newborn. These investigators, together with Kossman and Johnston, are the only one of the authors mentioned here, who have used the semidirect or unipolar leads. "While in the adults with normal heart

conditions," they say, "two different chest electrocardiograms—the left and the right—always exist, the newborn seem to show immediately after birth, usually over the whole thorax, only one pattern, that of the right chest electrocardiogram. This pattern changes in the left axillary line generally after a few hours, but

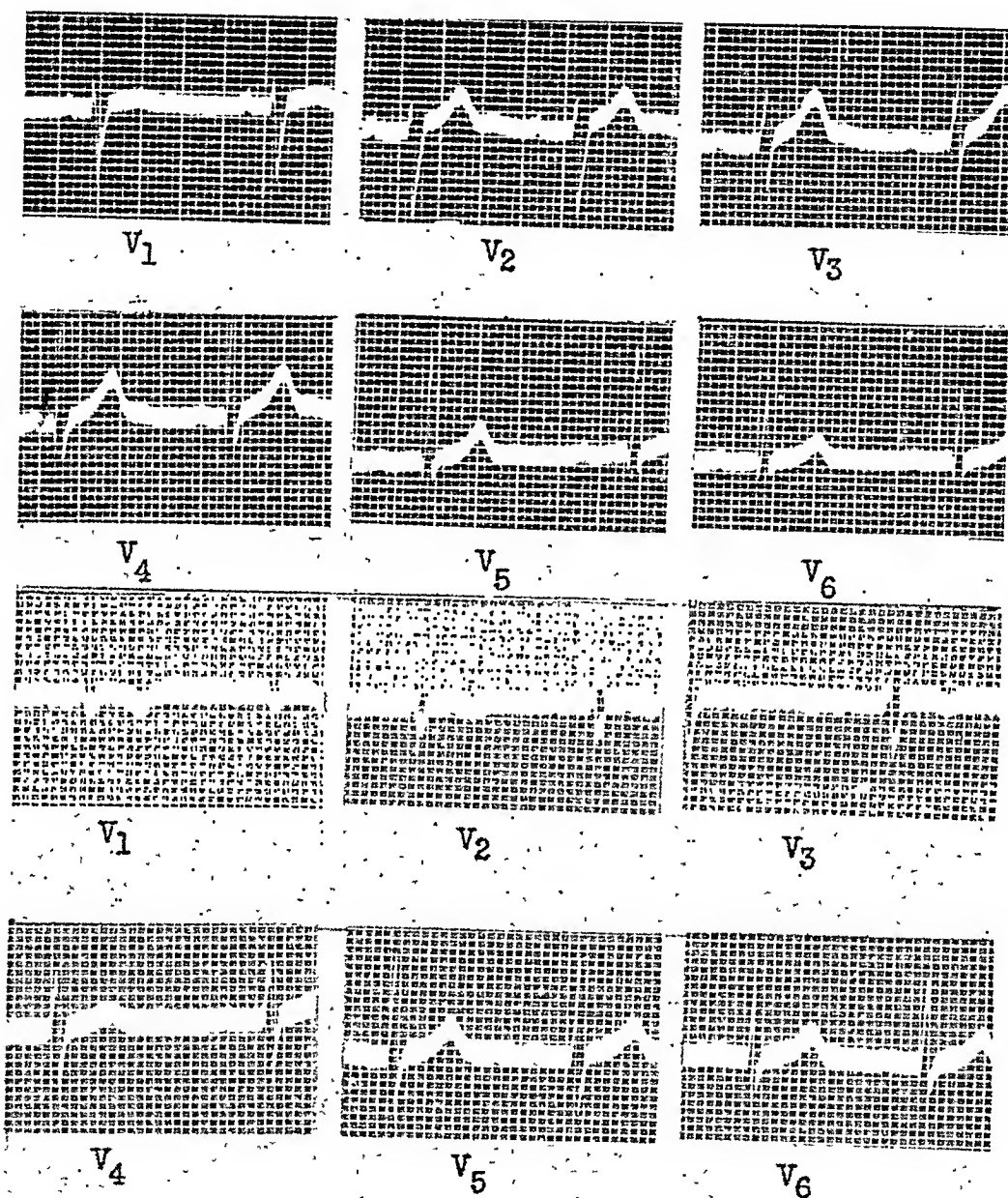


Fig. 4.—A, Case 986. M. V., aged 18 years, male. Adult type of electrocardiogram. Prolonged P-R interval in V₂, V₅, and V₆. B, Case 973. B. O., aged 15 years, male. Negative T wave in V₁, V₂, and V₃. Similar to child pattern, except for the relation of R height to S height.

not infrequently after days, into that of the left electrocardiogram. On the contrary, the chest electrocardiogram lead from the sternum does not change its character during the first life span; only the coefficient R-height to S-height alters insofar as, during the first days of life, the coefficient resembles that found

in older adults, while it changes later on to that found in children and younger adults."

It is therefore evident, from the literature just mentioned, that electrocardiographic studies have been made from before birth up to the ninth and tenth

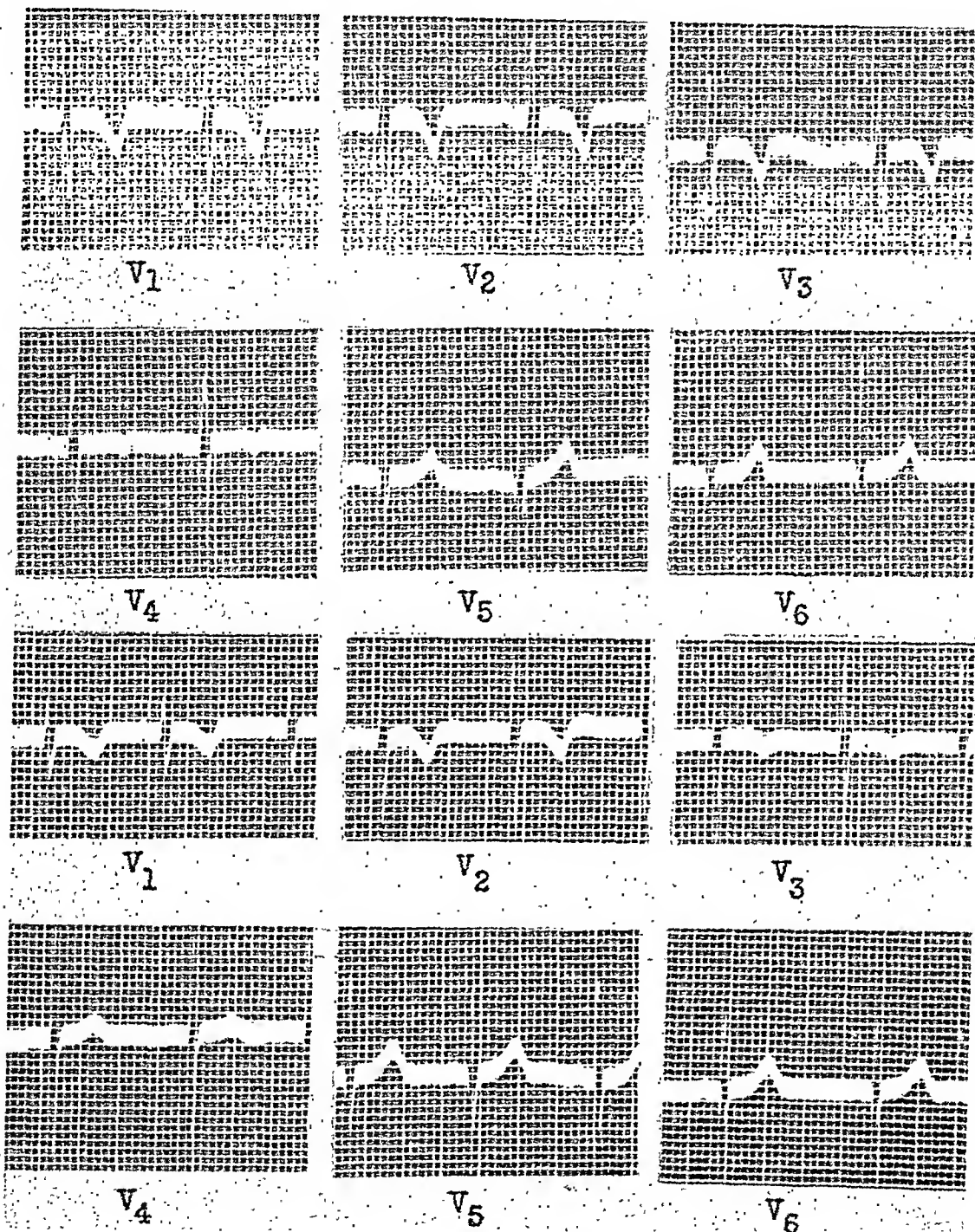


Fig. 5.—A, Case 963. A. L. P., aged 10 years, male. Negative and deep T wave in V_1 , V_2 , V_3 , and V_4 . B, Case 949. V. G., aged 8 years, male. Negative T wave only in V_1 , V_2 , and V_3 . Age alone is not the deciding factor.

decades of life. A gap exists, however. The age-group between 15 to 18 years has been overlooked or ignored by the investigators, or perhaps this group has simply been considered uninteresting, electrocardiographically.

It is a well-known fact that normal children often show inverted T waves in the leads from the right side of the precordium, but just how old the subject must be before such T waves should be regarded as probably abnormal has not been determined. We shall attempt to determine in this study, first, the approx-

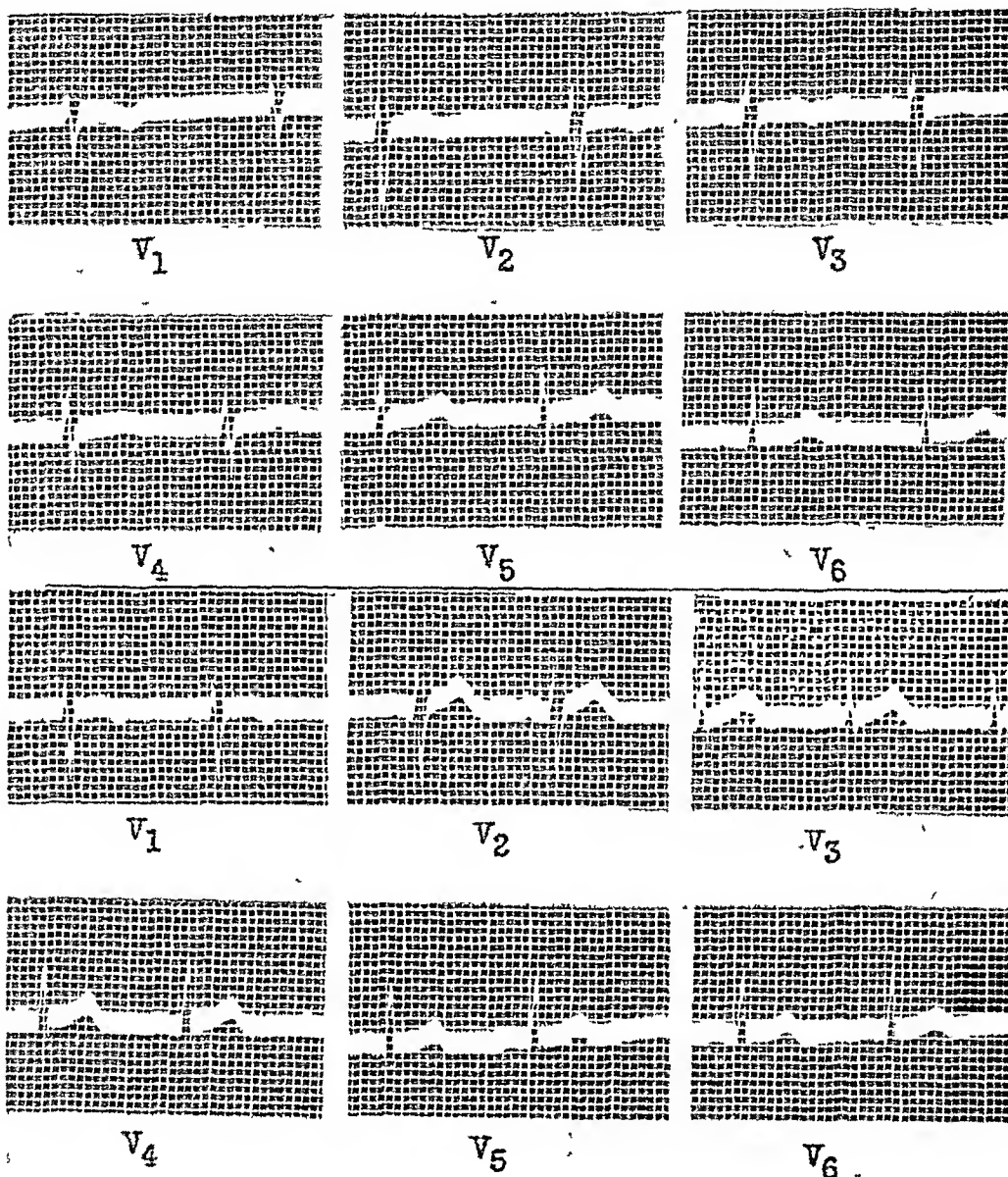


Fig. 6.—A, Case 938 G. M. G., aged 18 years, female. Negative T waves in V_1 , V_2 , and V_3 . B, Case 933. I. I. L., aged 17 years, female. Negative T wave only in V_1 . Although this patient was younger than the one in A, the adult pattern of the precordial electrocardiogram is present.

imate age at which a negative T wave may be considered abnormal and, second, whether or not the potential variations in the T wave are influenced by sex.

The T wave represents the main recession of the electrical impulse in the ventricle and is inscribed during ventricular contraction. It is the most unstable part of the electrocardiogram. Many physiologic conditions that will not affect

the QRS complex may alter the appearance of the T wave: heat and cold, digestion, change of position from the supine to the sitting or standing, nervous disturbances, and so forth. Cold applied to the apex will change a positive T wave

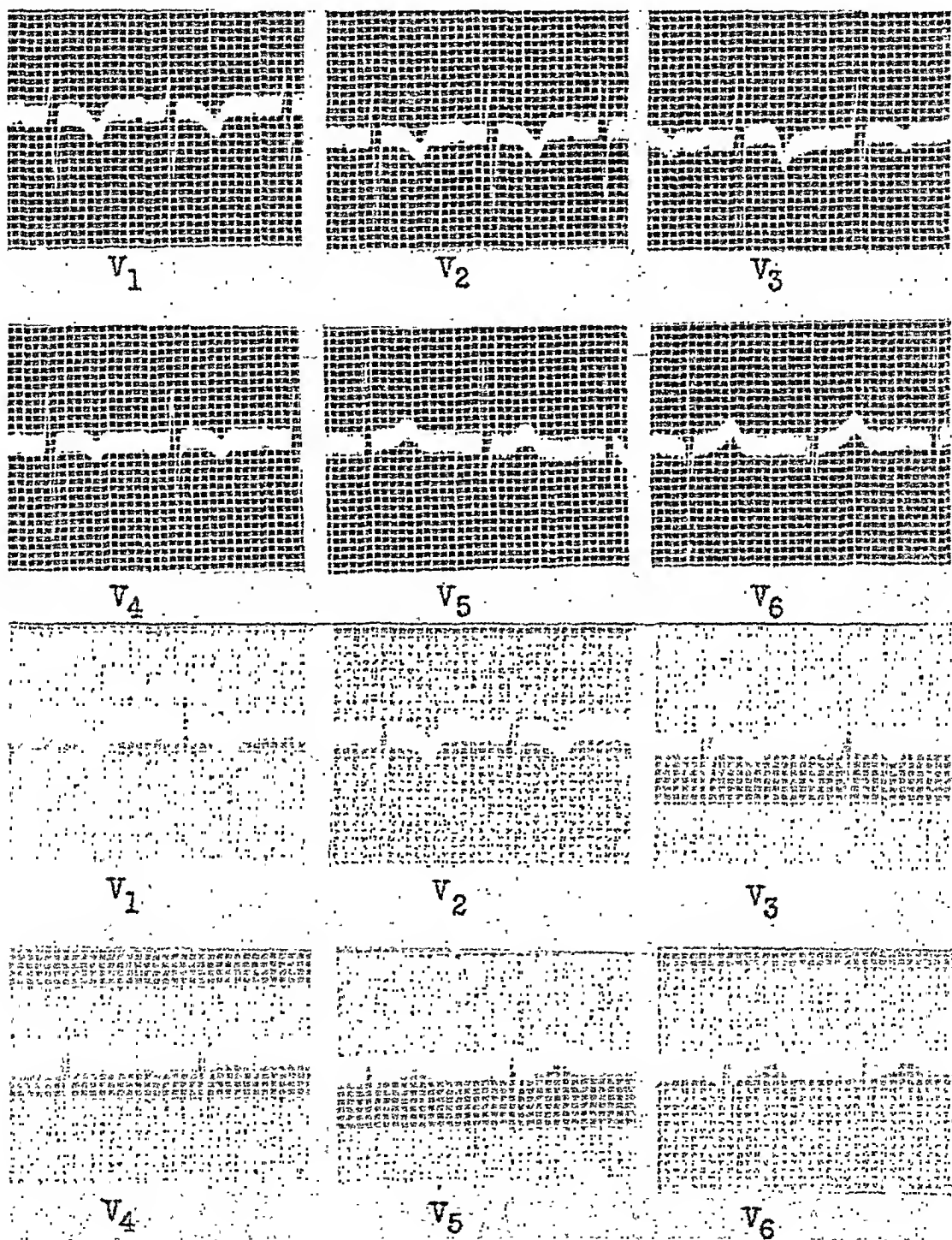


Fig. 7.—A, Case 7. R. N., aged 7 years, female. Negative T waves in V_1 , V_2 , V_3 , and V_4 . More marked negativity of T in V_4 than in patient in B, who is only 5 years of age. B, Case 3. M. C. B., aged 5 years, female. Negative T waves in V_1 , V_2 , V_3 , and V_4 .

to a negative one, because the cold shows the process of retreat. This has been shown by Wilson and Finch¹⁸ to occur in normal persons as a result of drinking cold water. Ashman and Hull,¹⁹ however, do not favor the idea that the sequence

TABLE I. T-WAVE SHAPE*

AGE AND SEX	NO.	V ₁	V ₂	V ₃	V ₄	V ₅	V ₆
Male adults 19-46 yr.	50	32 R 10 F 7 D \pm 1 D \mp	45 R 1 F 4 D \pm	48 R 2 P	44 R 6 P	47 R 3 P	50 R
Female adults 19-45 yr.	31	20 R 8 F 2 D \pm 1 D \mp	27 R 2 F 1 D 1 P	28 R 2 F 2 P	31 R	31 R	31 R
Male youngsters 12-18 yr.	20	19 R 1 D	12 R 1 F 5 D 1 P 1 Nt.	12 R 5 D 2 D 1 P 2 Nt.	18 R 2 D	20 R	20 R
Female youngsters 12-18 yr.	20	17 R 2 F 1 D	14 R 2 F 1 D	18 R 1 F 1 Nt.	20 R	20 R	20 R
Male children 5-11 yr.	20	18 R 2 D	9 R 11 D	9 R 10 D 1 Nt.	19 R 1 D	19 R 1 P	19 R 1 P
Female children 5-11 yr.	20	20 R	13 R 7 D	15 R 1 F 4 D	18 R 1 F 1 D	18 R 2 P	19 R 1 P

*R = Rounded, F = flat; D = diphasic; P = pointed; Nt. = notched.

TABLE II. T-WAVE DURATION (IN SECONDS)

AGE AND SEX	NO.	DURATION	V ₁	V ₂	V ₃	V ₄	V ₅	V ₆
Male adults 19-46 yr.	50	Min. Max. Av.	0.08 0.26 0.16	0.14 0.27 0.21	0.14 0.32 0.23	0.18 0.32 0.23	0.16 0.30 0.22	0.12 0.24 0.21
Female adults 19-45 yr.	31	Min. Max. Av.	0.06 0.20 0.136	0.08 0.24 0.167	0.10 0.28 0.196	0.12 0.28 0.190	0.12 0.24 0.181	0.12 0.20 0.161
Male youngsters 12-18 yr.	20	Min. Max. Av.	0.04 0.20 0.117	0.08 0.28 0.177	0.08 0.28 0.196	0.16 0.28 0.205	0.12 0.28 0.188	0.10 0.20 0.154
Female youngsters 12-18 yr.	20	Min. Max. Av.	0.08 0.18 0.115	0.08 0.20 0.155	0.12 0.24 0.175	0.16 0.24 0.175	0.12 0.24 0.167	0.12 0.20 0.155
Male children 5-15 yr.	20	Min. Max. Av.	0.12 0.18 0.128	0.08 0.18 0.141	0.08 0.24 0.142	0.10 0.24 0.179	0.16 0.24 0.191	0.16 0.20 0.177
Female children 5-15 yr.	20	Min. Max. Av.	0.12 0.18 0.149	0.08 0.16 0.136	0.08 0.26 0.157	0.08 0.24 0.181	0.12 0.24 0.178	0.12 0.20 0.178

of repolarization of the ventricular muscle is due to a difference in temperature; they are inclined to accept the suggestion of Dr. A. C. Young to the effect that the subendocardial muscle layers, being probably subjected to a higher pressure during systole than the subepicardial, may repolarize more slowly, particularly in the left ventricle and left side of the septum.

The ascending limb of the T wave rises slowly and inscribes a slight upward concavity; the descending limb comes down more abruptly. The apex, or peak, is therefore at a slightly greater distance from the base of the ascending limb than from that of the descending limb. In the negative wave, the descending limb descends more slowly with a tendency to inscribe an upward convexity, while the ascending limb rises more abruptly. The apex, or peak here, is farther away from the base of the descending limb than from that of the ascending limb. This apex, or peak, may be sharp and pointed, or more or less blunt. The wave may appear positive, isoelectric, diphasic, or negative.

Table I shows the shape or form of the T wave at the various precordial points: V_1 , V_2 , V_3 , V_4 , V_5 , and V_6 . "R" represents both the positive and negative T waves, when they are blunt or rounded. "F" represents the flat or isoelectric T waves; "D" the diphasic; "Nt." the notched; and "P" represents the pointed T waves of high voltage. In V_1 , both the children and the young boys and girls showed rounded T waves while only 64 per cent of the male and per cent of the female adults did. On the other hand, almost all the male and female adults showed the normal concavity of the T wave in V_2 , while only 60 per cent of the young boys, 70 per cent of the young girls, 45 per cent of the male and 65 per cent of the female children showed this form of T wave. The number of flat and diphasic T waves, which were more frequently observed at points V_2 and V_3 , diminished when we advanced to the left side of the heart so that in V_6 , all T waves appeared rounded or blunt in shape, except for one pointed T wave in the group of male and another in the group of female children. Most of the pointed and high T waves were observed in V_3 , V_4 , and V_5 of the group of male adults. There were more diphasic T waves in V_2 and V_3 of the group of male children than in any other group.

Although the duration of the T wave is probably of no particular importance and is difficult to measure accurately, we are reporting our findings in Table II. The duration of the T wave appears to be always less in V_1 than in V_6 of all groups, and slightly longer in the group of male adults than in all the other groups.

The voltage of the T wave appears in Table III. Each millimeter represents 0.20 millivolt. In order to express our results in millivolts, we would have to multiply the figures by 0.2. The highest T wave was 6.25 mm. in V_4 of the group of male adults; the lowest, -4.25 in V_2 of the group of male children. The wave appeared highest in V_4 and V_5 than at the other points, and higher in the adult males than in the adult females, and in the group of children than in the group of young boys and girls. The children and the adult males, therefore, exhibited the highest T waves in this series. With only one or two exceptions, the negative T wave was lower in V_1 than in V_2 . This is not the usual finding in coronary thrombosis.

In Table IV we have arranged the number of positive, negative, diphasic, and flat T waves found in the various groups. In V_1 , 18 men (36 per cent) and 16 women (51 per cent), 13 young boys (64 per cent) and 17 young girls

TABLE III. T-WAVE VOLTAGE IN MILLIMETERS (1 MM. = 0.20 MU.)

AGE AND SEX	NO	VOLTAGE	V_1	V_2	V_3	V_4	V_5	V_6
Male adults 19-45 yr.	50	Min. Max.	-2.5 2.5	0.5 5.25	1.25 6.00	2.00 6.25	1.25 5.00	0.50 4.00
Female adults 19-45 yr.	31	Min. Max.	-1.50 2.25	-1.25 3.00	-0.25 3.50	1.25 4.00	1.00 3.50	1.00 2.50
Male youngsters 12-18 yr.	20	Min. Max.	-2.50 1.25	-2.50 4.50	-0.75 4.25	1.00 4.00	1.00 4.50	1.00 4.25
Female youngsters 12-18 yr.	20	Min. Max.	-1.25 1.00	-0.75 3.00	-0.50 2.25	0.50 3.00	1.00 2.75	0.50 2.50
Male children 5-11 yr.	20	Min. Max.	-3.75 -0.75	-4.25 1.75	-3.00 1.50	-1.75 3.50	1.50 5.00	2.00 5.75
Female children 5-11 yr.	20	Min. Max.	-3.00 -1.00	-2.75 1.25	-2.00 3.00	-1.50 5.25	-1.00 5.00	1.25 3.50

TABLE IV. T WAVE; NUMBER OF POSITIVE, NEGATIVE, DIPHASIC, AND FLAT T WAVES

AGE AND SEX.	NO.	V_1	V_2	V_3	V_4	V_5	V_6
Male adults 19-46 yr.	50	18 - (36%) 8 D 10 F 14 +	0 - 4 D 1 F 45 +	All +	All +	All +	All +
Female adults 19-45 yr.	31	16 - (51%) 3 D 8 F 4 +	4 - 1 D 2 F 24 +	1 - 2 F 28 +	All +	All +	All +
Male youngsters 12-18 yr.	20	13 - (64%) 1 D 6 +	4 - 5 D 1 F 10 +	1 - 5 D 14 +	0 - 2 D 18 +	All +	All +
Female youngsters 12-18 yr.	20	17 - (85%) 1 D 2 F 0 +	2 - 1 D 2 F 15 +	1 - 1 F 18 +	All +	All +	All +
Male children 5-11 yr.	20	18 - (90%) 2 D 0 +	9 - 11 D 0 +	6 - 10 D 4 +	1 - 1 D 18 +	All +	All +
Female children 5-11 yr.	20	20 - (100%)	13 - 7 D 0 +	8 - 4 D 1 F 7 +	3 - 1 D 1 F 15 +	1 - 19 +	All +

(85 per cent), and 18 male (90 per cent) and 20 female (100 per cent) children showed a negative T wave.

In V_2 , there was no negative T wave for the group of male adults, but there were four diphasic and one isoelectric T wave. There were four negative T waves (13 per cent) in the group of female adults, with one diphasic and two flat or isoelectric; four (20 per cent) in the group of young boys, with five diphasic and one flat; two negative with one diphasic and two flat in the group of young girls; nine negative T waves (45 per cent) in the male children, with 11 diphasic; and 13 negative T waves (64 per cent), with seven diphasic in the group of female children. The frequency of negative T waves diminished rapidly from V_3 to V_6 , and there was not a single instance of negative T waves in V_6 .

In the group of male adults, negative T waves were observed only in V_1 (Figs. 1, 2, and 3). The groups of female adults and of the young boys and girls presented negative T waves in V_1 , V_2 , and V_3 . Several women between the ages of 18 and 34 showed negative T waves in V_1 and V_2 . The male children presented negative T waves as far to the left as point V_4 , one female child reaching point V_5 .

In general, it may be stated that negative T waves in the precordial electrocardiogram are more frequent in the female than in the male sex, except at the age level between 12 and 18 years, at which the incidence is similar. This may be explained by the fact that girls between 12 and 18 are more mature physically than boys of the same age.

Table V gives the percentages of all negative, diphasic, and flat T waves found at the various precordial points. The similarity existing between the groups of young girls and of the women, and the difference between the precordial electrocardiogram of the young boys and of the men, is again evident. Children, male and female, gave similar percentages, but there appears to be a slight tendency to more negative T waves in the girls.

TABLE V. T WAVE; PERCENTAGE OF NEGATIVE, DIPHASIC, AND FLAT T WAVES

AGE AND SEX	NO.	V_1	V_2	V_3	V_4	V_5	V_6
Male adults 19-46 yr.	50	72	10	0	0	0	0
Female adults 19-45 yr.	31	87	22	9	0	0	0
Male youngsters 12-18 yr.	20	70	50	30	5	0	0
Female youngsters 12-18 yr.	20	95	25	10	0	0	0
Male children 5-11 yr.	20	100	100	80	5	0	0
Female children 5-11 yr.	20	100	100	65	25	5	0

TABLE VI. S-T SEGMENT; NUMBER OF CASES AND NUMBER IN MM. ABOVE OR BELOW THE ISOELECTRIC LINE

AGE AND SEX	NO.	V ₁	V ₂	V ₃	V ₄	V ₅	V ₆
Male adults 19-46 yr.	50	4 + 1	6 + 1 1 + 1.5	7 + 1 1 + 1.5	7 + 1	1 + 1.5	1 - 1
Female adults 19-45 yr.	31	2 + 1	1 + 1 2 + 0.5	1 + 1 1 - 0.5	1 + 1	0	1 + 1
Male youngsters 12-18 yr.	20	0	1 + 1	1 + 1	1 + 1.25 1 + 0.5	1 + 1 1 + 0.5	1 + 0.5
Female youngsters 12-18 yr.	20	2 + 1 1 + 0.5	1 + 1 2 + 0.5	5 + 0.5	2 + 0.5	1 + 0.5	1 + 0.5
Male children 5-11 yr.	20	0	0	0	0	0	0
Female children 5-11 yr.	20	1 + 0.5	3 + 0.5	2 + 0.5	1 + 1 1 + 0.5	1 + 1 1 + 0.5	0 2 + 0.5

Only one case below isoelectric line -1 mm. in V₆ in a male adult.

Only two cases more than 1 mm. above isoelectric line (+1.25 mm.); in male youngster (18 years of age) and one male adult (+1.5 mm.).

S-T segment on line in all male children from 5 to 11 years of age.

Female children of the same age group showed slight deviation.*

Table VI reveals that deviation of the S-T segment from the isoelectric line was a relatively rare finding. Only one case, a male adult, showed negative deviation of 1 mm. (at point 6). The boys from 5 to 11 years showed no deviation of the S-T segment. The highest deviation (+1.5 mm.) was observed once in the group of male adults, but the usual deviation was from +0.50 to +1 millimeter.

We are also presenting the precordial electrocardiograms, obtained from two subjects of each of the groups studied, which show the various patterns at different age levels and the pronounced fluctuations in the T waves of different subjects of the same, or approximate, age (Figs. 1 to 7). The legend for each figure is self-explanatory.

SUMMARY AND CONCLUSIONS

We have presented a study of the T wave of the unipolar precordial electrocardiogram in 161 healthy Puerto Ricans, both male and female, between the ages of 5 and 46 years.

The form and voltage of the T wave, as well as the deviation of the S-T segment from the isopotential line, have been determined.

The study suggests that, independent of age levels and sex, a negative T wave in V₁ may be considered normal, and a negative T wave in V₆ should be considered abnormal.

In the male adult of over 19 years of age, a negative T wave in V₂, V₃, V₄, V₅, and V₆ is probably abnormal, especially at the last four points. In the adult

female of the same age, and in the young girls and boys 12 to 18 years of age, a negative T wave in V_4 , V_5 , and V_6 may be considered abnormal. In children from 5 to 11 years, a negative T wave is probably abnormal only when present in V_6 and perhaps V_5 .

Deviations of the S-T segment in the precordial electrocardiogram should be considered normal when such deviation is positive and does not go over 1.5 mm. in the adult or above 1 mm. in children. An S-T segment 1mm. below the isoelectric line was found only once—at point 6, in a male adult.

This study further suggests that, in addition to age and sex and such physiologic factors as cold, change of position, digestion, and nervous disturbances, there are other, yet undetermined, intrinsic factors that may influence the T wave of the precordial electrocardiogram in normal persons.

We are indebted to Dr. Frank N. Wilson, of Ann Arbor, Michigan, for having read this manuscript and offered valuable suggestions.

REFERENCES

1. Standardization of the Precordial Leads; Supplementary Report, *AM. HEART J.* 15: 235, 1938.
2. Willius, F. A.: The Heart in Old Age, *Am. J. M. Sc.* 182: 1, 1931.
3. Levitt, George: The Electrocardiogram in the Aged, *AM. HEART J.* 18: 692, 1939.
4. Taran, Leo M., and Kaye, Milton: Electrocardiographic Studies in Old Age, *Ann. Int. Med.* 20: 954, 1944.
5. Warnecke, B.: The Electrocardiogram in Apparently Non-Cardiacs Over 65 Years of Age, *Ztschr. f. Kreislaufforsch* 31: 391, 1931.
6. Gelman, I., and Brown, S.: Electrocardiographical Characterization of the Heart in Old Age and in Childhood, *Acta med. Scandinav.* 91: 378, 1937.
7. Shanno, Ralph L.: Variations in Normal Precordial Electrocardiograms, *AM. HEART J.* 19: 713, 1940.
8. Larsen, Kaj, and Skúlason, Th.: The Normal Electrocardiogram. I. Analysis of the Extremity Derivations From 100 Normal Persons Whose Ages Ranged From 30 to 50 Years, *AM. HEART J.* 22: 625, 1941.
9. Deeds, Douglas, and Barnes, Arlie R.: The Characteristics of the Chest Lead Electrocardiograms of 100 Normal Adults, *AM. HEART J.* 20: 261, 1940.
10. Thomas, C. B.: The Significance of Electrocardiographic Abnormalities in Young Adults, *Bull. Johns Hopkins Hosp.* 74: 229, 1944.
11. Graybiel, Ashton, McFarland, Ross A., Gates, Donald, and Webster, Fred: Analysis of the Electrocardiograms Obtained From 1,000 Young Healthy Aviators, *AM. HEART J.* 27: 524, 1944.
12. Kossman, C. E., and Johnston, Franklin D.: The Precordial Electrocardiogram. I. The Potential Variations of the Precordium and of the Extremities in Normal Subjects, *AM. HEART J.* 10: 925, 1935.
13. Bell, G. H.: The Human Fetal Electrocardiogram, *J. Obst. & Gynaec. Brit. Emp.* 45: 802, 1938.
14. Lepeschkin, E.: The Normal Chest Electrocardiogram in Childhood, *Arch. f. Kreislaufforsch.* 3: 321, 1938.
15. Master, Arthur M., Dack, Simon, and Jaffe, Harry L.: The Precordial Lead in Children. Presented at the Annual Scientific Meeting of the New York Committee on Cardiac Clinics, New York, N. Y., April 28, 1936.
16. Groedel, F. M., Kisch, B., and Reichert, P.: Changes in the Standard Electrocardiogram and the Chest Leads During the First Stages of Life, *Cardiologia* 6: 1, 1942.
17. Groedel, F. M., and Miller, Max: Electrocardiographic Studies in the Newborn, *Exper. Med. & Surg.* 2: 110, 1944.
18. Wilson, Frank N., and Finch, R.: Effect of Drinking Iced-Water Upon Form of T Deflection of Electrocardiogram, *Heart* 10: 275, 1923.
19. Ashman, R., and Hull, E.: Essentials of Electricardiography, New York, 1944, The Macmillan Co.

DISADVANTAGES OF THIOURACIL TREATMENT OF ANGINA PECTORIS

JOSEPH R. DiPALMA, M.D., AND JOHN J. MAgOVERN, M.D.

BROOKLYN, N. Y.

DESPITE the numerous reports¹⁻⁶ concerning the beneficial results to be obtained by total thyroidectomy for angina pectoris, this procedure has gained small popularity. With the advent of thiouracil,⁷ a drug capable of lowering oxygen consumption, even when the thyroid gland is normal,^{8,9} a means became available to reinvestigate this problem.

In 1944 we began to administer thiouracil to a limited number of cardiac patients with proved coronary artery disease and severe angina pectoris, keeping close watch on the level of oxygen consumption, the degree of anginal pain, and the exercise tolerance. Since then a publication¹⁰ has appeared which reports startlingly good results from this type of therapy. Our own results are not encouraging for the reasons to be outlined below, and it appears desirable to record them.

METHODS

Only patients who had been observed both on the wards and in cardiac clinic for several years were studied. This was desirable so that the subjective symptoms of angina pectoris might be better evaluated. Every clinician is acquainted with the variability of anginal pain, changing as it does with the season and the frame of mind of the patient. We desired to make sure of the consistency of the anginal pain of our patients by the best means available: a close personal acquaintance with the patient over an extended period of time.

All of the eight male patients included in this report had severe coronary artery disease. Electrocardiographic and clinical evidence indicated that six of them had had coronary occlusions with myocardial infarctions one to two years previous to the time of our study. The remaining two patients (Table I) gave no history of myocardial infarction. One patient, F. P., had a normal electrocardiogram at rest. However, after exercise the tracing showed marked depression of the S-T segment in Lead II, indicating marked myocardial ischemia. Moreover, both the systolic and diastolic blood pressure always fell after exercise. The second patient, L. P., was the only one of the group with a valvular lesion. He had severe rheumatic heart disease with marked aortic insufficiency. The

From the Department of Medicine, Long Island College of Medicine, Kings County Hospital Division.

Received for publication Feb. 28, 1946.

TABLE I. RESULTS OF THIOURACIL THERAPY IN EIGHT NONHYPERTENSIVE CARDIAC PATIENTS

PATIENT	AGE	DIAGNOSIS	DAILY DOSE OF THIOURACIL (GM.)	LENGTH OF TREATMENT	EXERCISE TOLERANCE (NO. OF FOOT-POUNDS)		CONTROL (B. M. R.)	MAXIMUM DEPRESSION OF B. M. R.	PRECORDIAL PAIN	RESULTS	COMMENT
					BEFORE TREATMENT	MAX. AFTER TREATMENT					
F. P.	55	Arteriosclerotic heart disease	0.6	59 days	5,100	7,395	+9	-11	No change	Poor	Toxic rash from thiouracil
I. F.	64	Arteriosclerotic heart disease	0.6	53 days	6,987	10,332	-7	+22	No change	Poor	Impossible to lower B. M. R. with dose used
M. G.	58	Arteriosclerotic heart disease	0.6	21 days	7,134	13,275	+45	+41	No change	Poor	Allergic to thiouracil, developed rash on two occasions
L. P.	34	Rheumatic heart disease; aortic insufficiency	0.6	26 days	7,380	30,012	+10	-10	Improvement, then severe recurrence	Poor	Developed severe dyspnea under treatment
F. T.	59	Arteriosclerotic heart disease	0.6	1 yr., 2 mo.	4,260	22,440	+55	-35	Marked improvement	Good	May be a case of masked hyperthyroidism
J. K.	51	Arteriosclerotic heart disease	0.6 to 0.8	1 yr., 1 mo.	14,520	33,278	-10	-20	Improvement, then recurrence	Poor	Developed symptoms of coronary occlusion on full doses of thiouracil
L. F.	54	Arteriosclerotic heart disease	0.6	1 yr., 1½ mo.	4,437	14,445	+25	-15	Marked improvement	Excellent	Able to resume work for a short period
N. S.	54	Arteriosclerotic heart disease	0.6 to 1.2	1 yr., 1½ mo.	3,949	13,266	0	-22	Limited improvement	Fair	Status anginosus; no real relief except at myxedema level

systolic blood pressure was 190 on the average; the diastolic pressure could not be determined since the sounds were still audible at zero. An electrocardiogram showed right bundle branch block. This, with the low diastolic pressure, may be taken as good evidence of myocardial ischemia. None of the patients were hypertensive.

Anginal pain was arbitrarily determined by assigning four degrees of severity of pain for each patient. Naturally, a 4 plus degree of pain for a patient with mild angina was not comparable to a 4 plus degree of pain in the patient with most severe angina. In grading the degree of pain, due consideration was given to the frequency of use of nitroglycerine and to various psychic influences.

An exercise test was done at suitable intervals, usually in the morning, two hours after a light breakfast. A single step nine inches high was used. The patient was always exercised at the rate of 20 to 25 steps per minute. Environmental temperature was kept at 70 to 74° F. Exercise was stopped only at the point of severe anginal pain. We found the exercise test particularly valuable because it enabled us to select patients from the viewpoint of angina rather than dyspnea as a limiting point to their exercise. The results were calculated in foot-pounds to obviate the factor of weight. Obviously a patient weighing 200 pounds doing 20 steps has done more work than a patient weighing 150 pounds doing the same number of steps. Also, with a lowering of the basal metabolic rate, the patients gain weight, and calculation of the results in foot-pounds of work done eliminates an obvious error from this factor.

Blood pressure and pulse rates at rest, immediately after exercise, and at intervals of two, four, and eight minutes after exercise were also taken. Since therapy had little effect upon these figures, they will not be reported.

Thiouracil* was generally administered in daily doses of 0.6 Gm. divided into three 0.2 Gm. portions. As much as 1.2 Gm. in divided daily doses was given to one patient (N. S.), but only while he was hospitalized. The patients were warned to watch for throat infections, fever, or rashes. They were seen weekly to prevent the signs and symptoms of agranulocytosis from escaping notice. None of them had palpable thyroid glands nor did any have the symptoms of hyperthyroidism. Patient F. T. (Table I) had an initial basal metabolic rate of +55 and may have had masked hyperthyroidism.

Placebo tablets resembling in every way the thiouracil tablets were used on two occasions to test the result of cessation of therapy without the patients' knowledge. These contained only small amounts of urea and magnesium sulfate to simulate the taste of thiouracil.

RESULTS

One of the first features to strike our attention was the refractory nature of the normal adult thyroid gland to thiouracil. This was particularly true when the control basal metabolic rate was near the zero level. In Table I it may be seen that patient F. P., after two months of 0.6 Gm. of thiouracil daily,

*Both the thiouracil and the placebo tablets used in this study were supplied through the generosity of Dr. Stanton B. Hardy of the Lederle Laboratories, Inc., Pearl River, N. Y.

had a drop of only from +9 to -11. Similarly, patient I. F. actually had a rise in the basal metabolic rate of from -7 to +22 on the same dosage. In his case considerable dyspnea was present during the final basal metabolic rate determination. This, however, we believe to be the result of a tendency of thiouracil to cause water retention;⁸ for this reason the result is valid and is properly included. In the case of M. G., therapy had to be stopped after three weeks because of a marked allergy to thiouracil. He developed a severe maculopapular rash which disappeared in two days. On restarting thiouracil the rash reappeared and therapy had to be terminated. Patient F. P. also developed a much more severe maculopapular rash with scaling, and therapy had to be stopped. It is interesting that in this latter case the rash occurred after thiouracil had been given for two months. Patient L. P. had a fall of the basal metabolic rate of from +10 to -10 on 0.6 Gm. of thiouracil daily for three and one-half weeks. In his case therapy had to be terminated because he acquired a severe constricting sensation in the chest and marked dyspnea, both exertional and nocturnal. In his case also we feel that the thiouracil caused water retention and incipient pulmonary edema, particularly in view of the severe aortic insufficiency.

In these four patients there was no real improvement in the degree of anginal pain. In the first three patients (Table I) exercise tolerance did not improve beyond what could be expected from training. The fourth patient, L. P., had an increase in exercise tolerance of from 7,380 foot-pounds to 30,012 foot-pounds. However, at the end of three weeks of therapy, he could not exercise at all because of dyspnea, so that no real gain was made.

The next four patients were treated for periods over one year and their cases will be described in detail.

CASE F. T. (Table I and Fig. 1).—Treatment was started on this patient in the middle of October, 1944. There was a marked fall in basal metabolic rate of from +55 to -22 after 0.6 Gm. of thiouracil daily for nine weeks. He did not suffer from Graves' disease so far as could be determined clinically. However, the elevated metabolism and especially the sensitivity to thiouracil strongly suggested that he had masked hyperthyroidism. The exercise tolerance quadrupled in the same period, and there was a marked diminution in precordial pain. Before therapy he had been using nitroglycerine daily; after therapy was started, it was required only occasionally. Toward the end of December he was put on placebo tablets for eight weeks. The metabolism then rose to -3. The exercise tolerance continued to improve, then fell sharply at the end of this period; that is, toward the last week of February. The precordial pain remained improved despite the rise in metabolism. He was again started on 0.6 Gm. of thiouracil daily to study the effects of a further lowering of metabolism. This time the thiouracil was continued without interruption for four months, until the end of June. The metabolic rate fell much more slowly this time, starting from a level of -7 and falling to -35 at the end of the period. He acquired definite symptoms of myxedema with a gain of 20 pounds in weight, lethargy, puffy face, and hoarse voice. The exercise tolerance improved at first during the months of March and April but fell gradually during May and June to pretherapy levels. The precordial pain disappeared completely from the end of March through July. In the exercise tolerance test, it is noteworthy that the limiting factor to exercise changed from precordial pain to dyspnea. Another interesting development was the onset of severe intermittent claudication during the period of the greatest depression of metabolism. Naturally, during this period the limiting factor to exercise was calf pain. This is explained by the marked diminution of peripheral blood flow which

is known to occur in myxedema.¹¹ During August and September thiouracil was not given. The metabolism promptly rose to zero in six weeks' time. The precordial pain returned. The exercise tolerance, however, did not improve appreciably.

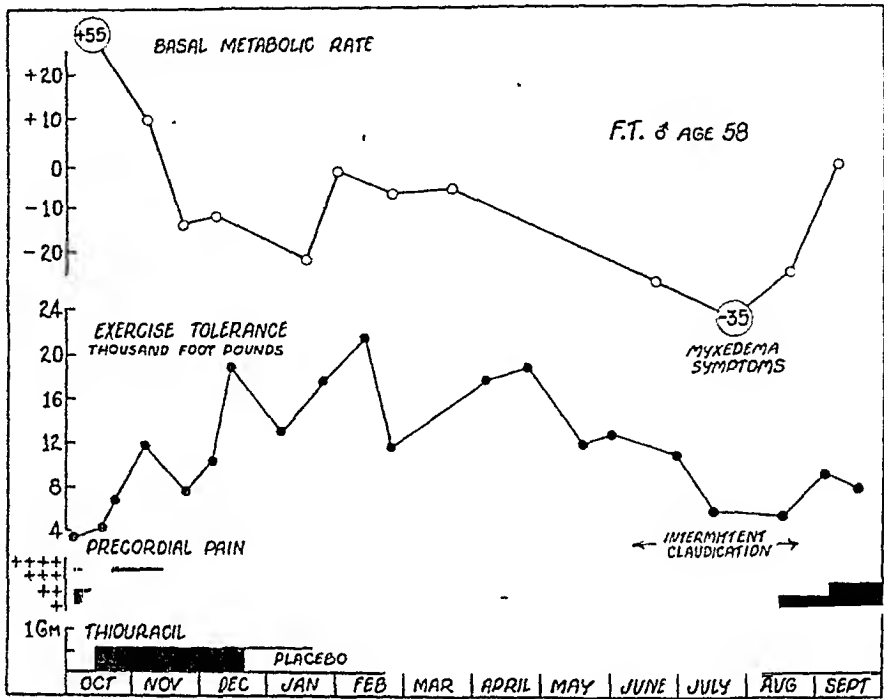


Fig. 1 — Effects of treatment in Patient F. T.

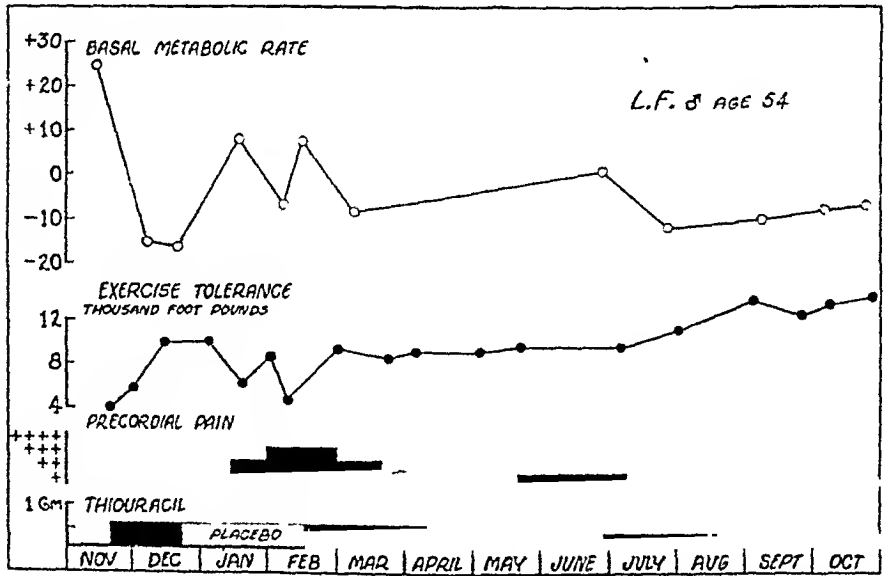


Fig. 2.—Effects of treatment in Patient L. F.

In summary, it may be said that the patient felt best and could do most when the basal metabolic rate was maintained between —10 and —20. Upon

cessation of thiouracil, his symptoms returned with the rising metabolism so that no real gain was made.

CASE L. F. (Table I and Fig. 2).—This patient had a control basal metabolic rate of +25 in November. With only four weeks' therapy with 0.6 Gm. of thiouracil daily, the basal metabolic rate fell to -15 in December. In this period, precordial pain diminished markedly and the exercise tolerance nearly tripled. When placed on placebo tablets, the metabolism rose to +8, fell to -6, and finally rose again to +8. At this time the exercise tolerance showed a closed inverse relationship to the level of metabolism. This was the only instance in the series in which it was possible to demonstrate clearly that when the level of metabolism rises, the ability to exercise falls, and vice versa. With the rise in metabolism the precordial pain returned. He was then put back on 0.6 Gm. of thiouracil daily in February. This was continued until May, when it was cut to 0.3 Gm. daily for one month, then raised to 0.4 Gm. daily until October. On these doses the metabolic rate was maintained at about -10. Precordial pain disappeared completely and the exercise tolerance improved steadily. The patient expressed great satisfaction and was able to return to light work for the first time in two years.

It must be pointed out in this case, however, that the thiouracil must be continued and the patient must be carefully watched to maintain the good results.

CASE N. S. (Table I and Fig. 3).—This was our patient with the most severe angina. He could only walk about fifty feet before he was seized with agonizing precordial pain. The control basal metabolic rate was zero. Starting in November, he was put on 0.8 Gm. of thiouracil daily for two weeks, then on 0.6 Gm. daily for two more weeks. The thiouracil then had to be stopped because of a severe upper respiratory infection. On this course of therapy the metabolism fell

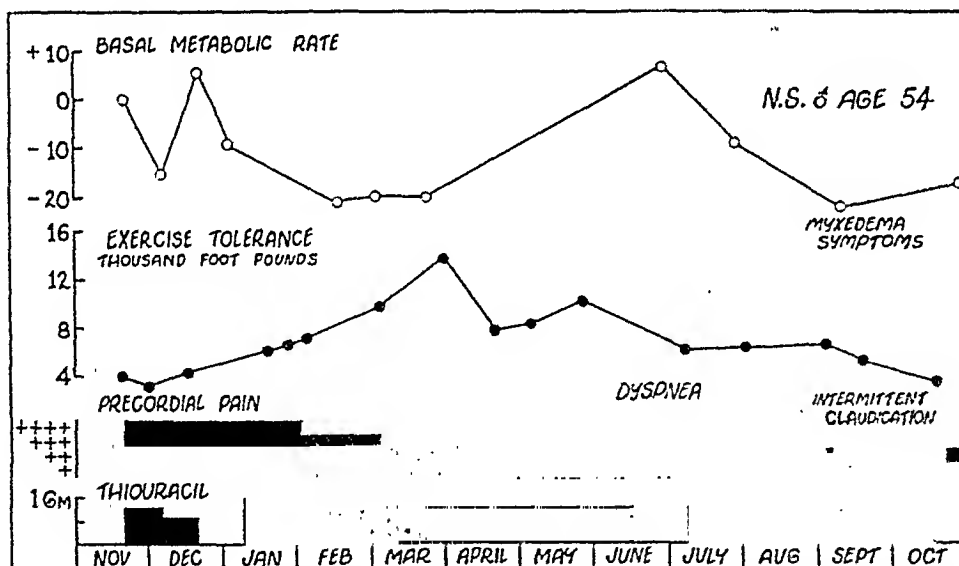


Fig. 3.—Effects of treatment in Patient N. S.

to -16. There was no change in precordial pain and exercise tolerance. It was decided to hospitalize him in January to give him an adequate course of thiouracil under close observation. He was given up to 1.2 Gm. of thiouracil daily in four doses for three weeks. This was then cut to 0.8 Gm. daily and maintained over a period of four and one-half months. At this time, in June, the drug had to be terminated because of the onset of severe nocturnal and exertional dyspnea. On this strenuous therapy the precordial pain diminished but little, although the metabolic rate attained a low of -20. The exercise tolerance improved up until April, when it had more

than tripled. After this period, ability to do exercise diminished gradually to control levels. In July the thiouracil was again started at a dosage level of 0.8 Gm. daily. In this instance the metabolic rate fell from +7 to -22, at which time (September) he had all the clinical signs of myxedema. In the entire one-year period, it was only at this time that he experienced any appreciable relief in the precordial pain. Ability to do exercise, however, was markedly curtailed because of the onset of severe intermittent claudication.

In summary, this patient with severe angina pectoris proved to be markedly refractory to thiouracil. A total dose of 209 Gm. of thiouracil over a period of 250 days was required to depress the basal metabolic rate to myxedema levels. Noteworthy is the fact that the control metabolic rate was zero. This brings out the point that the lower the metabolic rate is to begin with, the more difficult it is to depress it with thiouracil. No real gains were made either in improving the degree of precordial pain or in increasing exercise tolerance.

CASE J. K. (Table I and Fig. 4).—This patient had the least anginal pain of the group. He could walk from five to seven city blocks without pain. The control basal metabolic rate was the lowest of the group, -10. He also proved to be refractory to thiouracil. Daily dosage of from 0.6 to 0.8 Gm. only lowered the metabolic rate to -17 over a three-month period. The exercise tolerance more than doubled during this period. On the whole, the precordial pain dimin-

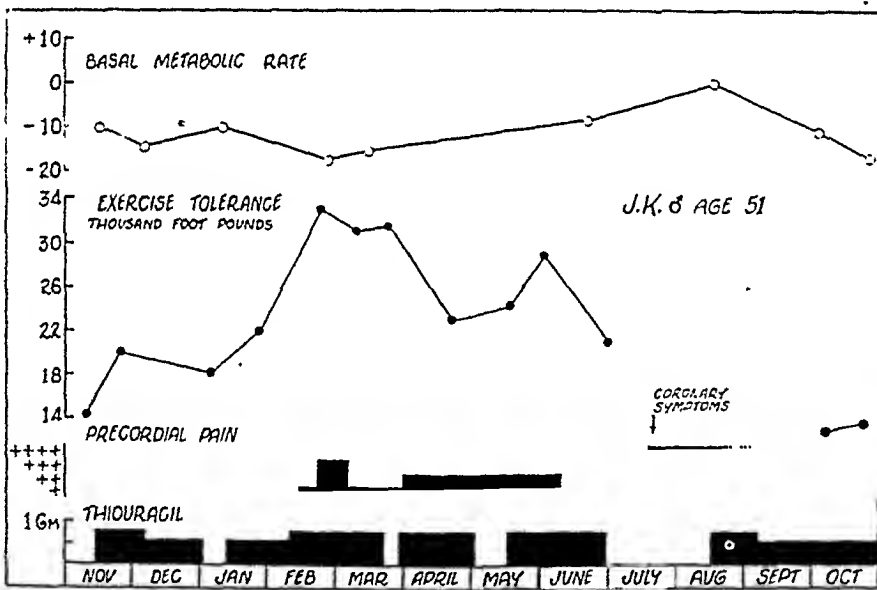


Fig. 4.—Effects of treatment in Patient J. K.

ished considerably, although he still experienced occasional severe attacks. Thiouracil was continued at 0.8 Gm. daily for four more months, until June, with two brief, free periods because of upper respiratory infections. The metabolic rate was not depressed but rose to -10 at the end of the period. For no apparent reason the exercise tolerance also diminished. In July he began to experience severe attacks of precordial pain. At the end of this month the pain became substernal in type and he was hospitalized for a period of bed rest and study. Three serial electrocardiograms did not reveal changes indicative of coronary occlusion, but the sedimentation rate was elevated and he had temperature rise to 101.4° F. which could not be explained. It

was therefore considered wise to treat him for myocardial infarction even in the absence of absolute proof. The precordial pain remained severe for the next four months in spite of the fact that readministration of thiouracil depressed the metabolic rate to -16 . When he was again exercised in October, he had returned to control levels.

In summary, this patient who had a low metabolic rate to begin with and relatively mild anginal pain may have been actually harmed by the thiouracil therapy. During the course of therapy he experienced symptoms of coronary occlusion. At the end of a year the anginal pain was worse and the exercise tolerance less than when therapy was started.

DISCUSSION

One point clearly brought out by this study is that depression of the basal metabolic rate diminishes precordial pain. This is most true in patients who have an initially elevated metabolism. Usually to make the precordial pain disappear completely, myxedema levels have to be attained. Thus the effects of total thyroidectomy on angina pectoris are reproducible by thiouracil therapy.^{1-6,12}

Does this mean that the coronary circulation is relatively enhanced in the states of diminished thyroid activity? The evidence is greatly against this viewpoint. In myxedema the cardiac output is diminished,¹³ blood volume is reduced,¹⁴ and the peripheral blood flow is slowed.¹¹ The individual's personality changes. He has less drive and less energy. Glandular activity and secretion is lessened. Intestinal absorption is slowed. Thus the beneficial results on coronary circulation could be explained purely on a mechanical basis: less demands are made upon a heart with diminished myocardial reserve. In other words, the individual is forced to live within the limits of his myocardium's ability to do work.

The attractive theory that diminished thyroid activity lessens the sensitivity of the heart to epinephrine has been enlarged upon.^{9,10} There is evidence against this theory,¹²⁻¹⁵ but, if proved true, it would be an added reason for diminishing thyroid activity in patients with heart disease.

There are, however, many practical disadvantages to both total thyroidectomy and thiouracil therapy. The difficulties of control of the basal metabolism by thyroidectomy have been pointed out.⁵ Thiouracil has proved to be rather toxic and no substitutes have been found for it.¹⁶ Moreover, it has to be given for long periods of time and in large doses in order to depress the metabolism of an individual whose metabolism is low initially. As soon as the drug is stopped, the metabolism rises again so that no real gain is made. The greatest difficulty is a tendency for water retention as metabolism is lowered. In certain cardiacs this results in pulmonary edema with nocturnal and exertional dyspnea.* Thus

*We were able to demonstrate this point clinically to our complete satisfaction. A patient with severe hypertensive heart disease and anasarca had been observed on the ward for at least six months. He was kept edema free only by injection of mercurials every third day and strict limitation of salt and fluid intake. Without changing his regimen in any way, he was given 0.6 Gm. of thiouracil daily. After six days he became markedly edematous and had an attack of severe pulmonary edema. The thiouracil was stopped and he promptly recovered. This experiment was repeated on two subsequent occasions with similar results. Thus the tendency of thiouracil therapy to cause water retention was amply demonstrated in this patient. The basal metabolism studies were unsatisfactory because the dyspnea obscured the results.

one defeats his purpose in these instances because obviously the patient is in more trouble with dyspnea than with angina.

It is well known that the amount of cholesterol in the blood rises with a lowering of the metabolic rate. Naturally this predisposes to atherosclerosis. Indeed, one of our patients developed symptoms strongly suggestive of coronary occlusion while on thiouracil therapy; in a former study,¹⁰ one of ten patients did have coronary occlusion. Therefore, there is a real possibility of actually harming a cardiac patient by lowering the metabolic rate even though the pain may be relieved.

Aside from these considerations, is the patient able to do more work after therapy? We found, as others have,¹⁻⁶ that the optimum effect in regard to exercise tolerance and well-being in general is obtained at a basal metabolic level ranging from -10 to -20 . Above this level the patients have too much anginal pain; below, they are too dull mentally and are apt to have intermittent claudication, as occurred in two of our patients. Even at the optimum level their ability to do work is not great and is sharply limited by a low myocardial reserve. The limiting factor to exercise simply changes from anginal pain to dyspnea or to a general tired feeling. Only one of our patients was able to resume light work. Certainly if a patient has anginal pain when his basal metabolism normally is -10 it would be foolhardy to attempt to improve his condition by further lowering his metabolism.

SUMMARY AND CONCLUSIONS

Thiouracil was administered to eight nonhypertensive cardiac patients with various degrees of anginal pain. All of them had normally functioning thyroid glands, except one who may have had masked hyperthyroidism. Six of these patients had previous coronary occlusion. The seventh had definite electrocardiographic changes indicative of coronary disease after exercise, and the eighth had rheumatic heart disease with severe aortic insufficiency and bundle branch block.

The relationship between the level of metabolic rate, the degree of precordial pain, and exercise tolerance was followed in each patient. In four of the patients, therapy was stopped after periods ranging from three weeks to two months for the following reasons; toxic skin rashes in two instances, onset of severe exertional and nocturnal dyspnea, and failure to lower the basal metabolic rate with the dosage used. No real benefit on either precordial pain or exercise tolerance was experienced by any of these four patients.

The four remaining patients were treated and followed for over a year. In two of them it was possible to attain myxedema levels. In general, precordial pain was beneficially affected, at least for a period of time, in each of these patients; at certain times exercise tolerance was doubled and even quadrupled. However, all of them except one lost his increased ability to do work at the end of the one-year period. One patient had symptoms resembling coronary occlusion during the course of therapy.

The disadvantages of thiouracil as a drug for use in patients with normally functioning thyroid glands may be listed as follows: toxicity of the drug, necessity for close supervision of the patient over long periods of time, inability to lower metabolism when the basal metabolism is low to start with, tendency toward water retention, particularly deleterious in cardiac patients, and necessity for continual therapy in order to maintain results.

Thiouracil therapy for angina pectoris is therefore not recommended as a routine procedure. It is indicated in angina pectoris, when the basal metabolic rate is elevated, and can be used as a therapeutic test by those who wish to select patients with angina pectoris for thyroidectomy.

REFERENCES

1. Blumgart, H. L., Levine, S. A., and Berlin, D. D.: Congestive Heart Failure and Angina Pectoris: The Therapeutic Effect of Thyroidectomy on Patients Without Clinical or Pathological Evidence of Thyroid Toxicity, *Arch. Int. Med.* 51: 866, 1933.
2. Blumgart, H. L., Berlin, D. D., Davis, D., Riseman, J. E. F., and Weinstein, A. A.: Total Ablation of the Thyroid in Angina Pectoris and Congestive Failure. XI. Summary of Results in Treating Seventy-Five Patients During the Past Eighteen Months. *J. A. M. A.* 104: 17, 1935.
3. Clark, R. J., Means, J. H., and Sprague, H. B.: Total Thyroidectomy for Heart Disease. Experience With Twenty-one Patients at the Massachusetts General Hospital, New England *J. Med.* 214: 277, 1936.
4. Cutler, E. C., and Schnitker, M. T.: Total Thyroidectomy for Angina Pectoris, *Ann. Surg.* 100: 578, 1934.
5. Friedman, H. F., and Blumgart, H. L.: Treatment of Chronic Heart Disease by Lowering Metabolic Rate. The Necessity for Total Ablation of the Thyroid, *J. A. M. A.* 102: 17, 1934.
6. Claiborne, T. S., and Hurxthal, L. M.: Results of Total Thyroidectomy in Heart Disease. *New England J. Med.* 216: 411, 1937.
7. Astwood, E. B.: Chemotherapy of Hyperthyroidism. The Harvey Lectures, Lancaster, Pa., 1944-1945, Science Press Printing Co.
8. Williams, R. H., Bissel, G. W., Jandorf, B. J., and Peters, J. B.: Some Metabolic Effects of Thiouracil With Particular Consideration of Adrenal Functions, *J. Clin. Endocrinol.* 4: 58, 1944.
9. Raab, W.: Diminution of Epinephrine Sensitivity of the Normal Heart Through Thiouracil, *J. Lab. & Clin. Med.* 30: 774, 1945.
10. Raab, W.: Thiouracil Treatment of Angina Pectoris, *J. A. M. A.* 128: 249, 1945.
11. Stewart, H. J., and Evans, W. F.: Peripheral Blood Flow in Myxedema, *Arch. Int. Med.* 69: 808, 1942.
12. Riseman, J. E. F., Gilligan, D. R., and Blumgart, H. L.: Treatment of Congestive Heart Failure and Angina Pectoris by Total Ablation of the Normal Thyroid Gland. XVI. The Sensitivity of Man to Epinephrine Injected Intravenously Before and After Total Thyroidectomy, *Arch. Int. Med.* 56: 39, 1935.
13. Stewart, H. J., Deitrick, J. E., and Crane, N. F.: Studies of the Circulation in Patients Suffering From Spontaneous Myxedema, *J. Clin. Investigation* 17: 237, 1938.
14. Gibson, J. G., II, and Harris, W. H.: Clinical Studies of the Blood Volume. II. Hyperthyroidism and Myxedema, *J. Clin. Investigation* 18: 65, 1939.
15. DiPalma, J. R., and Dreyer, N. B.: Failure of Thiourea to Alter the Autonomic Responses of Intact Animals, *Endocrinol.* 36: 236, 1945.
16. Astwood, E. B.: Some Observations on the Use of Thiobarbital as an Antithyroid Agent in the Treatment of Graves' Disease, *J. Clin. Endocrinol.* 5: 345, 1945.

CARDIOVASCULAR DEFECTS IN SELECTIVE SERVICE REGISTRANTS

COLONEL RICHARD H. EANES, M.C., UNITED STATES ARMY, AND KENNETH H. MCGILL, A.B., AND MARDELLE L. CLARK, A.B., WASHINGTON, D. C.

CARDIOVASCULAR defects have consistently ranked among the five leading causes for rejection of men liable for military service who were physically examined through the Selective Service System since 1940. Some cardiovascular defect was considered the most important cause for rejection of one in every fourteen men disqualified for military service at the end of 1944. In addition, approximately the same ratio of the World War II veterans who were receiving disability pension awards in the fall of 1944 had cardiovascular defects as their major disability.

The widespread prevalence of heart defects among men 18 through 44 years of age is not surprising, since heart disease is the leading cause of death among men between the ages of 25 and 44 and third in importance as a cause of death among those 15 through 24 years of age. These defects were found in 83 of every thousand registrants examined by Selective Service local board physicians during 1940 and 1941, the peacetime period of Selective Service operation. Valvular heart disease (rheumatic and syphilitic) and arterial hypertension were the most frequent diagnoses recorded, as well as the leading causes for rejection of Selective Service registrants during both peacetime and wartime.

The Armed Forces' standards for acceptance of registrants with cardiovascular defects have undergone only slight changes since 1940.* Differences

From the Medical Division and the Division of Research and Statistics, National Headquarters, Selective Service System.

This report is based on sample studies of the results of examinations recorded on DSS Form 200, Reports of Physical Examination, for Selective Service registrants physically examined at local boards during 1940-1941, and DSS Form 221, Reports of Physical Examination and Induction, for registrants examined at local boards and induction stations during 1942-1944. Coverage of the sample studies varied from 10 to 25 per cent of the examinations. Additional data on cardiovascular defects among Selective Service registrants are contained in the following bulletins published by National Headquarters of the Selective Service System: Folk, O. H., McGill, K. H., and Rowntree, L. G.: Medical Statistics Bulletin No. 1, Analysis of Reports of Physical Examination, Nov. 10, 1941; Edwards, T. I., McGill, K. H., and Rowntree, L. G.: Medical Statistics Bulletin No. 2, Causes of Rejection and Incidence of Defects, An Analysis of Reports of Physical Examination From 21 Selected States, Aug. 1, 1943; Greve, C. H., McGill, K. H., and Rowntree, L. G.: Medical Statistics Bulletin No. 3, Physical Examination of Selective Service Registrants During Wartime, Nov. 1, 1944.

Received for publication Dec. 31, 1945.

*The cardiovascular standards for acceptability of Selective Service registrants are contained in War Department Mobilization Regulations 1-9: Standards of Physical Examination During Mobilization. In general, the only cardiovascular defects which were acceptable were (a) a pulse rate of 100 or over if not persistent and not due to paroxysmal tachycardia; (b) a pulse rate of 50 or under which is proved the natural rate, or a temporary rate, or due to drugs; (c) sinus arrhythmia; and (d) temporary elevation of blood pressure due to excitement. A pulse rate of 50 beats per minute became unacceptable in April, 1944, but the change had little effect on the rate of rejection of registrants. No registrants with cardiovascular defects were acceptable for limited service.

in examining procedures, however, as well as in application of the cardiovascular criteria, produced differences both in the rates of rejection for cardiovascular defects and in the diagnoses of certain specific defects in the group. During 1940 and 1941, all the registrants receiving physical examination were examined by local board physicians, who were usually general practitioners. Most of the rejections during this time occurred at the local board level. The physical standards were high, and most of the rejections were made on diagnoses of physical rather than mental defects. The situation was reversed beginning in early 1942, when physical standards were lower, particularly in reference to dental and visual defects, and local board physicians rejected only those registrants with the more serious defects which were manifestly disqualifying. After that, most of the rejections were made by specialists at the induction stations, where psychiatric examinations, blood pressure readings, and other special tests were given only as a part of the routine examination at the Armed Forces' induction stations.

The rates of rejection for cardiovascular defects presented in this discussion and their relative importance as causes for rejection are based on their occurrence as the most serious defects for which the registrants were rejected. The tables showing the prevalence of these defects among all registrants include, in addition to the principal causes for rejection, disqualifying heart defects which were secondary causes for rejection and also the less serious heart defects such as transient hypertension, arrhythmias, and functional murmurs.

NUMBER CURRENTLY REJECTED

Among the nearly five million registrants who were classified as unfit for any form of military service as of January 1, 1945, an estimated 300,100, or 6.7 per cent, had been rejected because the principal defect was cardiovascular (Table I). This figure includes not only the registrants in Class 4-F on that date, but also those who had been rejected for cardiovascular defects and later reclassified in occupationally deferred classes because they were in essential industry or agriculture. It does not include, however, registrants who had been rejected for cardiovascular defects who were re-examined at a later date and inducted or were again rejected for a primary cause which was not cardiovascular.

TABLE I. ESTIMATED NUMBER OF REGISTRANTS AGED 18 TO 37 YEARS IN REJECTED CLASSES BECAUSE OF CARDIOVASCULAR DEFECTS,* JAN. 1, 1945

RACE	TOTAL IN REJECTED CLASSES	REJECTED FOR CARDIOVASCULAR DEFECTS	
		NUMBER	PERCENTAGE OF TOTAL
All races.....	4,493,000	300,100	6.7
White†.....	3,621,000	250,900	6.9
Negro.....	872,000	49,200	5.6

*Includes registrants in Class 4-F and also those transferred from Class 4-F to the occupationally deferred classes, 2-A (F), 2-B (F), and 2-C (F).

†Includes all races other than Negro.

Registrants who were rejected for cardiovascular defects were the fourth group in order of importance, exceeded only by those rejected for mental disease, mental deficiency, and musculoskeletal defects. Relatively more white than Negro registrants who were rejected had cardiovascular defects as the principal cause for their rejection.

The specific diagnosis in more than four of every ten rejections for cardiovascular defects was valvular heart disease, most of which was rheumatic in origin. Arterial hypertension was recorded as the diagnosis in three of every ten cardiovascular rejections.

REJECTION RATES FOR CARDIOVASCULAR DEFECTS

The number of registrants rejected for cardiovascular defects decreased from 44 of every thousand registrants physically examined in 1940 and 1941 to 35 per thousand examined in 1944 (Table II). Much of the decrease was the result of the changes in examining procedure discussed previously, which gave an increased value to and a resulting increase in the rate of rejection for neuropsychiatric defects. Other factors, which also effected a decrease in rejection rates for all defects combined, were: (1) changes in the age composition of the group which was subject to induction into the Armed Forces; (2) lower standards for acceptance, particularly those pertaining to dental and visual defects and educational deficiency, during wartime; (3) a Presidential order at the end of 1942, prohibiting the direct enlistment of men 18 through 37 years of age at Armed Forces' recruiting stations.* This cessation of voluntary enlistments made available for examination through Selective Service a large number of physically fit registrants who would not otherwise have been represented in Selective Service data.

TABLE II. ESTIMATED REJECTION RATES FOR CARDIOVASCULAR DEFECTS, BY RACE, 1940-1944*

YEAR	ALL RACES	WHITE†	NEGRO
1940-1941.....	43.6	44.1	39.6
1942.....	35.0	33.8	42.5
1943.....	29.1	27.3	38.6
1944.....	34.7	33.4	43.5

*Rate per 1,000 examined.
†Includes all races other than Negro.

Among white registrants, the rates of rejection for cardiovascular defects decreased from 44 of each thousand examined in 1940 and 1941 to 33 per thousand examined in 1944. On the other hand, Negro cardiovascular rejection rates tended to increase during wartime, when the majority were examined at induction

*During 1940-1941, the ages of men designated as liable for military service were 21 through 35 years; during 1942, they were 20 through 44 years; and in the two succeeding years, registrants 18 through 37 years were liable, with increasing emphasis during 1944 on the induction of men under 26 years of age.

stations where routine blood pressure readings were made. This is borne out by the fact that hypertension was responsible for almost one-half the Negro cardiovascular rejections during the first two wartime years.

SPECIFIC DIAGNOSTIC GROUPS OF CARDIOVASCULAR DEFECTS

Although cardiovascular defects were recorded on the physical examination reports of 83 registrants in every thousand examined by local board physicians during 1940 and 1941 (Table III), they were the most important causes for rejection of only 44 per thousand examined. They were noted either as secondary causes for rejection or as minor or functional defects in the remaining 39 cases per thousand. The more serious defects, such as valvular heart disease, were almost invariably cause for rejection, so their rates of prevalence and rejection were approximately equal. On the other hand, arrhythmias, functional murmurs, and tachycardia were more important among the total number of physically examined registrants than among those rejected.

TABLE III. PREVALENCE OF CARDIOVASCULAR DEFECTS AND PERCENTAGE DISTRIBUTION OF REJECTIONS FOR THESE DEFECTS AMONG REGISTRANTS PHYSICALLY EXAMINED AT LOCAL BOARDS, 1940-1941*

MAJOR SUBGROUP	PREVALENCE PER 1,000 EXAMINED			PERCENTAGE DISTRIBUTION OF REJECTIONS		
	ALL RACES	WHITE†	NEGRO	ALL RACES	WHITE†	NEGRO
Total cardiovascular....	83.1	84.6	71.8	100.0	100.0	100.0
Rheumatic and valvular.	28.4	28.5	26.0	44.1	44.6	40.0
Hypertension, arterial...	16.6	16.3	19.1	31.6	30.6	40.0
Tachycardia, persistent..	6.7	7.2	3.0	8.4	8.8	5.0
Cardiac hypertrophy....	2.8	2.8	3.0	2.5	2.5	2.5
Cardiac arrhythmia.....	5.5	5.8	3.8	1.8	1.8	1.3
Cardiovascular diseases, other‡.....	4.1	4.3	2.8	6.5	6.7	5.0
Functional murmurs....	5.0	5.2	4.3	0.6	0.6	0.5
Other cardiovascular defects§.....	14.0	14.5	9.8	4.5	4.4	5.7

*Corresponding data for induction stations are not available for the period 1940-1941.

†Includes all races other than Negro.

‡Includes diseases of the heart and vascular system in which the physician recorded a diagnosis other than rheumatic heart disease, valvular heart disease, hypertension, hypertrophy, tachycardia, or arrhythmia.

§Includes entries describing signs, symptoms, or diseases of the heart and circulatory system not elsewhere classifiable, such as: bradycardia, arteriosclerosis, arterial hypotension, and hypertension or tachycardia described as nervous or functional in type.

Valvular heart disease was the most frequently recorded cardiovascular defect. It occurred in 28 of every thousand registrants examined during peacetime. Rheumatic fever was specified as the etiology in only 4 per thousand of

these cases.* The valvular heart disease category also included diagnoses of defects of specified valves and systolic murmurs unspecified as to type. These unspecified systolic murmurs accounted for almost 10 per cent of all the cardiovascular defects recorded. In 79 per cent of the cases where the valve was specified (excluding definite rheumatic heart disease) the mitral valve was affected, in 14 per cent the aortic valve was affected, and in 4 per cent both the aortic and the mitral valves were affected. Endocarditis, which is frequently preceded or accompanied by rheumatic involvement, was recorded for less than one registrant in every thousand examined.

The prevalence rate of such cardiovascular defects as hypertension, tachycardia, cardiac arrhythmias, murmurs, and hypertrophy is slightly understated, for the reason that they were often recorded as observations on which a specific diagnosis of organic heart disease was based. In these cases, the more serious diagnosis was counted. Hypertension was recorded as the chief diagnosis in approximately 20 cases per thousand, 3 per thousand of which were regarded as transient in type. Tachycardia was third in relative frequency among the cardiovascular defects recorded, but it was noted as the most important diagnosis for 13 registrants in every thousand examined and was specified as functional tachycardia in nearly one-half of these cases. The functional type of tachycardia, as well as transient hypertension, is included in the miscellaneous group of cardiovascular defects shown in Table III.

Cardiovascular defects were noted more often for white than for Negro registrants. Of the specific defects, the valvular heart disease group was almost equally important in the two races. Cases diagnosed as being rheumatic in origin, however, occurred almost three times as often among the white registrants as they did among Negroes.

Of all the registrants who were rejected for cardiovascular defects during peacetime, almost one-half had valvular heart disease. Approximately 3 in 10 had hypertension as the principal cause for rejection. No other single defect approached this relative importance among cardiovascular rejections, the nearest being tachycardia, which accounted for about one in 12 of the cardiovascular rejections.

The importance of the various cardiovascular defects as causes for rejection of white registrants was similar to that of all races. Among Negroes, however, hypertension assumed first place, accounting for 4 in every 10 Negro cardiovascular rejections.

The changes in examining procedure which began in 1942 resulted in important changes in the diagnoses of specific cardiovascular defects. The first of these, resulting from the routine psychiatric examination at induction stations, produced a shifting of diagnoses from the cardiovascular to the psychiatric category. Thus, conditions which during peacetime were recorded by local board physicians simply as tachycardia were diagnosed by psychiatrists as paroxysmal

*Acute rheumatic fever was found infrequently among Selective Service registrants, since men with this condition seldom came up for physical examination until the acute stage had subsided. It was diagnosed in 0.1 per thousand registrants examined during 1940 and 1941, probably through affidavits from the registrants' personal physicians.

tachycardia or neurocirculatory asthenia. The prevalence of tachycardia (including functional) decreased by almost one-third under this procedure, while that of paroxysmal tachycardia and neurocirculatory asthenia tripled between 1940 and 1944.

The second change, occasioned by the routine blood pressure readings at induction stations, affected the relative importance of the specific defects within the cardiovascular group. As hypertension was diagnosed more frequently, it increased both in recorded prevalence and in importance as a principal cause for rejection, and there was a corresponding decrease in most of the other specific defects.

A third factor which affected the prevalence rate for cardiovascular defects in wartime was that fewer minor heart disturbances appeared in the physician's summary of defects from which the wartime figures were obtained. This largely accounted for the decrease in recording of all heart defects from the peacetime figure of 83 to the wartime figure of 51 per 1,000 examined.¹ The relative importance of the more serious defects, however, was approximately the same as during peacetime.

Hypertension and valvular heart disease were the defects most frequently found, the former in 18.4 cases per thousand examined and the latter in 16.5 (Table IV). Tachycardia, next in frequency, was tabulated in only 4.5 cases per thousand.

Cardiovascular defects occurred in 50 of every thousand white registrants examined and in 58 per thousand Negroes. This higher rate of prevalence among the Negroes reflects the more frequent diagnoses of hypertension for that race.

TABLE IV. PREVALENCE OF CARDIOVASCULAR DEFECTS AND PERCENTAGE DISTRIBUTION OF REJECTIONS FOR THESE DEFECTS AMONG REGISTRANTS PHYSICALLY EXAMINED AT LOCAL BOARDS AND INDUCTION STATIONS, 1942-1943

MAJOR SUBGROUP	PREVALENCE PER 1,000 EXAMINED			PERCENTAGE DISTRIBUTION OF REJECTIONS		
	ALL RACES	WHITE*	NEGRO	ALL RACES	WHITE*	NEGRO
Total cardiovascular	51.0	49.8	57.7	100.0	100.0	100.0
Rheumatic and valvular	16.5	16.6	16.2	44.7	46.6	36.5
Hypertension, arterial	18.4	16.7	27.5	35.5	32.8	47.3
Tachycardia, persistent	4.5	4.8	2.7	6.1	6.7	3.5
Cardiac hypertrophy	1.8	1.7	2.7	3.6	3.3	4.5
Cardiac arrhythmia	0.6	0.6	0.5	0.3	0.4	0.3
Cardiovascular diseases, other†	2.4	2.4	2.3	5.9	6.3	4.2
Functional murmurs	3.6	3.8	2.8	0.3	0.3	0.2
Other cardiovascular defects‡	3.2	3.2	3.0	3.6	3.6	3.5

*Includes all races other than Negro.

†Includes diseases of the heart and vascular system in which the physician recorded a diagnosis other than rheumatic heart disease, valvular heart disease, hypertension, hypertrophy, tachycardia, or arrhythmia.

‡Includes entries describing signs, symptoms, or diseases of the heart and circulatory system not elsewhere classifiable, such as: bradycardia, arteriosclerosis, arterial hypotension, and hypertension or tachycardia described as nervous or functional in type.

Cardiac hypertrophy was the only other cardiovascular defect recorded more frequently for Negro than for white registrants.

As in peacetime, the most important causes for rejection were the valvular heart disease group and arterial hypertension. These two defects accounted for 80 per cent of the wartime cardiovascular rejections. The two defects combined were less important for white registrants than for Negroes, but the diagnosis of valvular heart disease was far more important among the white race and that of hypertension was more important among the Negroes. Tachycardia accounted for relatively one-half as many Negro as white rejections for cardiovascular defects.

CARDIOVASCULAR SYPHILIS AND VARICOSE VEINS

Cardiovascular defects described as due to syphilis have been included in the syphilis category rather than under cardiovascular defects in Selective Service data. However, the prevalence of cardiovascular defects in which syphilis was specified as the etiology was low during both the peacetime and the wartime periods. The incidence was 0.3 per thousand registrants examined for all races, 0.1 for whites, and 1.7 for Negroes. It accounted for only 0.1 per cent of the rejections during each period.

Varicose veins were noted in 32 registrants of every thousand examined during 1940 and 1941, but during wartime they were included in the summary by induction station examiners in only 16 cases per thousand. They were responsible for little more than 1 per cent of the rejections.

CARDIOVASCULAR REJECTIONS IN RELATION TO AGE

Rejection rates for cardiovascular defects increased with increasing age. The relative importance of specific diagnoses as causes for rejection, however, differed in the various age groups. This is illustrated in Table V, which indicates the relative importance of the three leading cardiovascular diagnoses among registrants rejected in 1944.

Hypertension and valvular heart disease were almost equally important among all registrants rejected for cardiovascular defects; each accounted for more than 4 in every 10 of these rejections. Tachycardia accounted for less than one in 10 cardiovascular rejections.

A review of the percentages of rejections for the specific defects in the various age groups shows that hypertension increased sharply with increasing age; that valvular heart disease was *less than one-half as important among men 30 years of age and over as among the 18-year-old registrants*; and that the proportion rejected for tachycardia was relatively constant in each age group.²

Hypertension was the only cardiovascular subgroup of less relative importance as cause for rejection of white registrants than of all races; for Negroes, it was the only defect more important for them than for all races. It accounted for 40 per cent of the white as compared to 67 per cent of the Negro cardiovascular rejections.

TABLE V. PERCENTAGE OF CARDIOVASCULAR REJECTIONS DUE TO SPECIFIC DIAGNOSES, BY AGE AND RACE*

AGE (YR.)	TOTAL	PERCENTAGE OF CARDIOVASCULAR REJECTIONS FOR			
		ARTERIAL HYPERTENSION	RHEUMATIC AND VALVULAR HEART DISEASE	TACHY- CARDIA	OTHER
<i>All Races</i>					
All ages.....	100.0	43.7	42.4	6.7	7.2
18.....	100.0	14.0	69.4	6.1	10.5
18-25.....	100.0	35.5	49.2	8.0	7.3
26-29.....	100.0	44.1	43.7	6.3	5.9
30 and over.....	100.0	52.7	33.8	6.4	7.1
<i>White†</i>					
All ages.....	100.0	38.9	45.7	7.7	7.7
18.....	100.0	9.5	72.7	6.5	11.3
19-25.....	100.0	28.9	54.4	9.0	7.7
26-29.....	100.0	38.8	47.6	7.4	6.2
30 and over.....	100.0	48.8	36.4	7.3	7.5
<i>Negro</i>					
All ages.....	100.0	67.0	26.0	2.2	4.8
18.....	100.0	39.8	51.1	3.4	5.7
19-25.....	100.0	61.8	29.0	3.8	5.4
26-29.....	100.0	67.5	26.6	1.5	4.4
30 and over.....	100.0	74.8	19.4	1.3	4.5

*Based on a sample of Reports of Physical Examination and Induction for registrants inducted or rejected during February, 1944, through May, 1944.

†Includes all races other than Negro.

In general, the distribution of the various cardiovascular defects as causes for rejection in each racial category followed the same trends as for all races. Hypertension increased in relative importance with increasing age; valvular heart disease decreased sharply as age increased, and tachycardia decreased only slightly.

OCCUPATIONS OF CARDIOVASCULAR REJECTEES

The occupational distribution of registrants rejected because of cardiovascular defects is shown in Table VI. Selective Service policies regarding occupational deferments affect the representativeness of certain of these major occupational groups, however, notably the farm owners and farm laborers. Their physical and mental defects are probably less representative of the farmers in the general population than of those in other occupations, since the Tydings Amendment to the Selective Training and Service Act late in 1942 resulted in widespread occupational deferments in the agricultural groups, without physical examination.

TABLE VI. PERCENTAGE OF REJECTIONS IN MAJOR OCCUPATIONAL GROUPS
BASED ON CARDIOVASCULAR DEFECTS*

OCCUPATION	PERCENTAGE OF REJECTIONS IN EACH OCCUPATION GROUP DUE TO CARDIOVASCULAR DEFECTS		
	ALL RACES	WHITE†	NEGRO
All occupations.	9.2	9.2	9.3
Professional and semiprofessional.	12.1	12.1	†
Farm owners, managers, and laborers.	6.9	6.9	6.8
Proprietors, managers, and officials.	12.7	12.7	†
Clerical, sales, and kindred.	11.5	11.4	†
Craftsmen and foremen.	9.9	9.8	12.3
Operatives.	9.5	9.2	11.6
Service workers.	10.5	10.5	†
Laborers, except farm.	7.9	6.4	9.9
Students.	15.1	14.8	†
Emergency workers and unemployed.	4.7	5.0	3.9
Nonclassifiable and not stated.	7.2	7.2	7.2

*Based on a sample of Reports of Physical Examination and Induction for registrants examined during February, 1944, through April, 1944.
†Includes all races other than Negro.
‡Negro rates not presented for occupations with less than 2 per cent of total Negro rejections.

Cardiovascular defects accounted for 9 per cent of the rejections in all occupations, with approximately the same proportions of white and Negro rejections made for these defects. Only three occupational groups, the farm owners and laborers, other laborers, and the emergency workers and unemployed, had relatively fewer cardiovascular rejections than the average for all occupations.

Students had the highest proportion of rejections for cardiovascular defects. These were the principal defects of almost one in every 6 of the student rejections. Approximately one in every 8 rejections in the professional group and in the managerial and official group were made because of cardiovascular defects. Among emergency workers and the unemployed, at the lowest extreme, only one in 20 was rejected for cardiovascular defects.

Among white registrants, cardiovascular rejections in each occupational group were similar to those for all registrants. Relatively more Negro than white registrants who were craftsmen and foremen, operatives, and laborers were rejected for cardiovascular defects.

RE-EXAMINATION OF REGISTRANTS WITH CARDIOVASCULAR DEFECTS

Early in Selective Service experience the question arose as to whether any considerable number of men who had been found disqualified for military service might have been rejected on mistaken diagnoses. In order to determine the probable amount of salvage of such men, and also to make possible a detailed analysis of current problems in cardiovascular diagnosis, a re-examination study was made by special medical advisory boards in five of the largest cities in

the country. This study, covering re-examination of 4,994 men formerly rejected because of cardiovascular defects and neurocirculatory asthenia, was conducted by members of the Subcommittee on Cardiovascular Diseases, National Research Council, who were appointed as members of special Selective Service Medical Advisory Boards.³

Of the 4,994 men who were re-examined, 17.3 per cent were resubmitted as qualified for general military service, while the remaining 82.7 per cent were retained in the rejected classification. In view of the relatively small percentage of registrants reclassified for induction, the time required for re-examination, and the scarcity of expert examiners during wartime, the wisdom of extending the re-examination of registrants rejected for cardiovascular defects was considered doubtful.

The five leading causes for rejection, in order of their importance, were: rheumatic heart disease, found on first examination in 50 per cent of the total 4,994, and diagnosed for 59.9 per cent of those rejected after re-examination; arterial hypertension; neurocirculatory asthenia; sinus tachycardia; and congenital heart disease.

Several problems in diagnosis raised by the study were posed for further research, possibly in a follow-up of the borderline cases. Chief among these were questions of (1) interpretation and significance of apical systolic murmurs; (2) the possible need for extending the upper limits of blood pressure standards in very nervous young men to 160 mm. or slightly higher, provided the diastolic pressure does not exceed 90 mm.; extending the limits of pulse rates at rest to approximately 40 to 120 per minute; and expanding the limits on heart size. The usefulness of exercise tests in cardiovascular examination for military service was also questioned.

SUMMARY

Some of the more important facts derived from Selective Service experience in the physical examination of men with cardiovascular defects may be summarized as follows:

1. Cardiovascular defects are among the leading causes for rejection of Selective Service registrants. Among men in the rejected classes, they are the fourth group in order of importance, exceeded only by mental disease, mental deficiency, and musculoskeletal defects.

2. More than 300,000 registrants, or 6.7 per cent of the total in the rejected classes on Jan. 1, 1945, had heart defects as the most serious defect. The percentage of white registrants with these defects was larger than that of Negroes.

3. Valvular heart disease (rheumatic and syphilitic) and arterial hypertension have been the leading specific causes for cardiovascular rejection, as well as the most frequently recorded cardiovascular defects, during both peacetime and wartime. Valvular heart disease occurred more frequently among white registrants, while hypertension was a much more important diagnosis among the Negroes.

4. Within the various age groups, rejections for rheumatic-valvular heart disease decreased as age increased; it was particularly important among 18-year-old registrants, accounting for nearly 70 per cent of their cardiovascular rejections during a four-month period in 1944.

5. Arterial hypertension became more important as a cause for rejection with increasing age. Among registrants 30 years old and over who were rejected because of cardiovascular defects it accounted for more than one-half the rejections. Less than one-half the white rejections 30 years of age and over were made for this cause, however, while three-fourths of the Negroes in this age group who were rejected for cardiovascular defects had arterial hypertension.

6. Emergency workers, the unemployed, and farmers had the lowest percentages of rejections for cardiovascular defects; students had the highest percentage of rejections for these defects.

REFERENCES

1. Edwards, T. I., and Hellman, L. P.: Methods Used in Processing Data From the Physical Examination Reports of the Selective Service System, *J. Am. Statistical Association* 39: 165, 1944.
2. Rowntree, L. G., McGill, K. H., and Edwards, T. I.: Causes of Rejection and Incidence of Defects Among 18 and 19 Year Old Registrants, *J. A. M. A.* 123: 181, 1943.
3. a. Levy, R. L., Stroud, W. D., and White, P. D.: Report of Re-examination of 4,994 Men Disqualified for General Military Service Because of the Diagnosis of Cardiovascular Defects, *J. A. M. A.* 123: 937, 1943; *ibid.*, 123: 1,029, 1943.
b. Fenn, G. K., Kerr, W. J., Levy, R. D., Stroud, W. D., and White, P. D.: Re-examination of 4,994 Men Rejected for General Military Service Because of the Diagnosis of Cardiovascular Defects, *AM. HEART J.* 27: 435, 1944.

Clinical Reports

ACUTE PERICARDITIS SIMULATING CORONARY ARTERY OCCLUSION

CAPTAIN CHARLES W. COFFEN, M.C., AND MAJOR MAXWELL SCARF, M.C.
ARMY OF THE UNITED STATES

ACUTE pericarditis of infectious origin may present various clinical patterns. Its existence is often undetected because the symptoms and signs are weighed with those of the underlying disease. Occasionally, its onset is manifested by severe precordial pain and shock, simulating an acute coronary occlusion. Cases of this type have been described by Barnes and Burchell.¹ Differentiation between the two conditions is, of course, important because of the difference in their management and prognosis. In a recent small series of cases of acute pericarditis simulating coronary occlusion which were reported by Wolff,² mention was made of the presence of a slow pulse as a differentiating feature of pericarditis. Recently we saw a patient with severe precordial pain, shock, and slow pulse in whom myocardial infarction was suspected but in whom further study led to a diagnosis of acute pericarditis. The case is presented because this particular clinical picture is not well known.

CASE REPORT

A 26-year-old Army officer came to the hospital at 8 A.M. on Oct. 5, 1944, with the presenting symptom of intense substernal pain which had awakened him three hours earlier. The pain radiated to both shoulders, was aggravated by breathing, and prevented him from assuming a recumbent position. He had previously been in good health and there was no history suggesting that he had ever had rheumatic fever, tuberculosis, coronary insufficiency, trauma to the chest, or a recent respiratory infection.

Preliminary examination revealed a young man who did not appear ill except that he was unable to lie flat on the examining table because of pain in the anterior midchest. No abnormality of the heart, lungs, or thoracic wall could be detected. The blood pressure was 120/80 and the heart rate, 72 per minute. During the examination a sudden and dramatic change occurred in the appearance of the patient. The face became ashen and the lips cyanotic. The heart rate fell to 38 per minute, the rhythm became irregular, and the sounds almost inaudible. The blood pressure could not be measured. The skin became covered with a cold, drenching sweat. This alarming situation improved gradually after the administration of morphine sulfate. The pulse slowly increased to 60 per minute and the blood pressure to 90/60. The patient was transferred to a hospital bed where he was placed in a sitting position and in an oxygen tent. Two more doses of morphine were necessary to control the pain which remained severe until noon. Six hours after admission the patient was completely free of pain and could lie flat without dis-

comfort and without the use of oxygen. He presented a normal appearance. The heart sounds were clearer, the rate was 80 per minute, the rhythm was regular, and the blood pressure was 120/80. This respite, however, was brief, and a few hours later cyanosis reappeared, the heart rate increased to 130 per minute, and the temperature rose to 100° Fahrenheit. Fortunately resumption of oxygen therapy was followed by an amelioration of symptoms after several hours. The following morning the temperature, pulse rate, and blood pressure reached normal levels where they remained for the duration of the patient's hospital stay. At this time a pericardial friction rub became audible over the lower sternum. The friction rub disappeared in several hours and made its final appearance the following day for a short time. The further course of the patient was uneventful. No evidence of pericardial effusion or cardiac enlargement was observed. The patient was kept in bed for four weeks and returned to his usual duties after a short convalescent leave.

The leucocyte count was 16,700 on the day of admission, 12,150 on the following day, and subsequently normal. The blood sedimentation rate by the Westergren method was 64 mm. in one hour and did not approach normal limits until the twelfth hospital day. The most important laboratory findings were revealed by the electrocardiograms. As will be seen in Fig. 1, *A*, the S-T segments are slightly elevated in Leads I and II without reciprocal S-T₃ deviation. Small

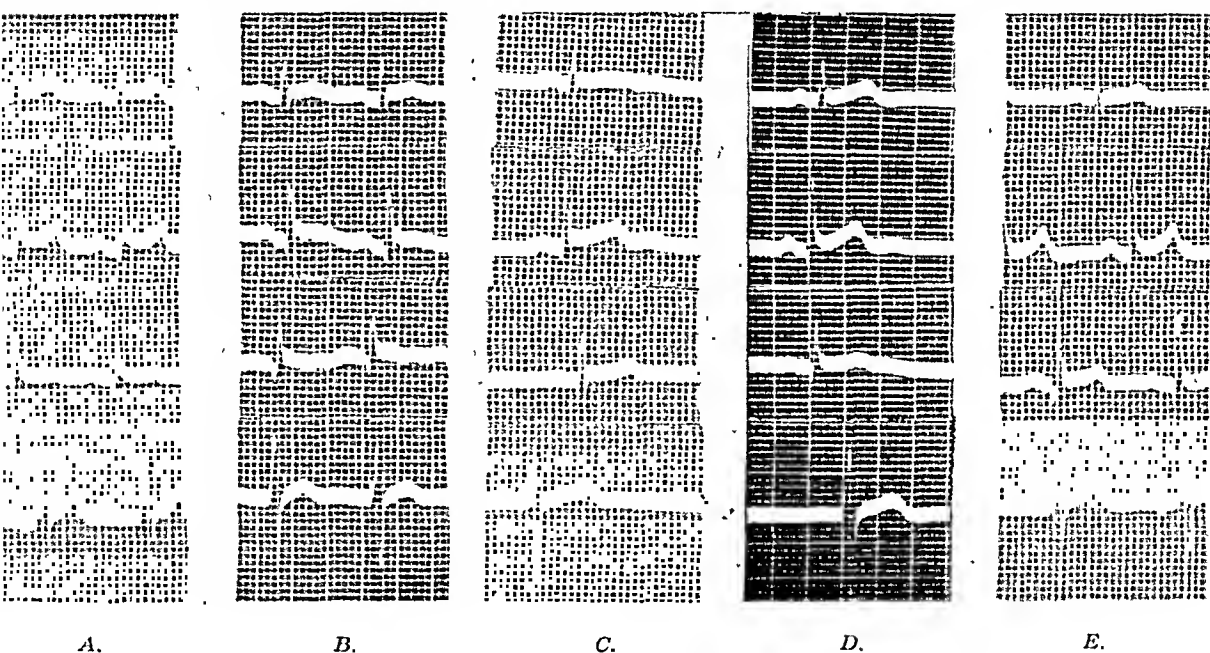


Fig. 1.—The electrocardiograms consist of the three standard limb leads and Lead CR₄. The findings are discussed in the text. *A*, Taken Oct. 5, 1944; *B*, Oct. 6, 1944; *C*, Oct. 9, 1944; *D*, Oct. 13, 1944; *E*, March 3, 1945.

Q₂ and Q₃ waves are present. In Fig. 1, *B*, elevated S-T segments are present in all limb leads and the T waves in all leads are of lower amplitude. Lead CF₄ is normal. *C* and *D* of Fig. 1 are representative of subsequent electrocardiograms and show no changes characteristic of myocardial infarction, the only abnormality present being S-T segment elevation in the indirect leads.

Spontaneous mediastinal emphysema or pneumothorax as a cause of the clinical picture³ and electrocardiographic changes⁴ were precluded by the normal roentgenograms of the chest and the absence of relevant clinical findings.

Approximately six months after the onset of the illness, the patient appeared for a routine examination. He had been asymptomatic throughout this period of time. Physical examination of the heart revealed no abnormalities. Roentgen examination of the heart was likewise normal. An electrocardiogram taken at this time (Fig. 1, *E*) showed that slight elevation of the S-T segments in Leads II and III was still present.

COMMENT

At the time the patient had severe substernal pain, shock, and cyanosis, he appeared critically ill. It is natural to associate this picture with an acute myocardial infarction. Criteria favoring a diagnosis of acute pericarditis, however, were present and included the youth of the patient. A significant characteristic of the pain was its aggravation by breathing and change of position. This rarely occurs in infarction of the myocardium. The slow pulse rate mentioned by Wolff² was also present. The transitory friction rub and fever were more suggestive of myocardial infarction than pericarditis because in the latter condition these signs tend to be present from the onset and are more persistent. Finally, the electrocardiographic changes were characteristic of acute pericardities.¹

Collapse with slow pulse and low blood pressure may have been the result of increased vagal tone caused by the pericarditis or by the pleuritis which is frequently associated with it. A similar reflex vagal stimulation is occasionally observed following puncture of the chest wall (so-called pleural shock) or during abdominal operations.

The presence of fever, leucocytosis, and an elevated blood sedimentation rate was considered evidence for an infectious origin of the pericarditis. No specific etiologic factor, however, was present. Rheumatic fever, tuberculosis, septicemia, uremia, and disseminated lupus erythematosus are usually revealed by clinical characteristics not present in the case described. Barnes and Burchell¹ have observed young adults with a benign and apparently limited form of pericarditis possibly caused by tuberculosis. Acute pericarditis may be associated with infections of the upper respiratory tract⁵ and sinuses⁶ and may complicate primary atypical pneumonia.⁷ It has also been described following operative procedures^{8,9} and in epidemic form.¹⁰ In one series of cases,¹ evidence of an upper respiratory tract infection was found in 57 per cent of patients. In the remaining 43 per cent, as in our case, no causative agent was demonstrated.

CONCLUSION

A case report of acute pericarditis of unknown etiology is presented to illustrate that the clinical picture may be one of intense precordial pain associated with shock and a strikingly slow pulse. Vagal stimulation of reflex nature from the inflamed pericardium is suggested as the cause of the collapse and slow pulse. Acute pericarditis may closely simulate acute coronary occlusion.

REFERENCES

1. Barnes, A. R., and Burchell, H. B.: Acute Pericarditis Simulating Acute Coronary Occlusion: A Report of Fourteen Cases, *AM. HEART J.* **23**: 247, 1942.
2. Wolff, L.: Acute Pericarditis Simulating Myocardial Infarction, *New England J. Med.* **230**: 422, 1944.
3. (a) Scott, A. M.: The Significance of the Anginal Syndrome in Acute Spontaneous Pneumomediastinum, *Lancet* **1**: 13, 1937.
(b) Hamman, L.: Spontaneous Mediastinal Emphysema (Henry Sewall Lecture), *Bull. Johns Hopkins Hosp.* **64**: 1, 1939.
(c) Hamman, L.: Mediastinal Emphysema, *J. A. M. A.* **128**: 1, 1945.
4. Miller, H.: Spontaneous Mediastinal Emphysema With Pneumothorax Simulating Organic Heart Disease, *Am. J. M. Sc.* **209**: 211, 1945.
5. Willius, F. A.: Clinic on Acute Serofibrinous Pericarditis Secondary to Acute Pharyngitis: Comment; Treatment; Course, *Proc. Staff Meet., Mayo Clin.* **9**: 637, 1934.
6. Comer, M. C.: Acute Pericarditis With Effusion: A Sequel to Sinusitis, *Southwestern Med.* **11**: 310, 1927.
7. Finklestein, D., and Klainer, M. J.: Pericarditis Associated With Primary Atypical Pneumonia, *AM. HEART J.* **28**: 385, 1944.
8. Butsch, W. L.: Acute Pericarditis as Postoperative Complication, *Proc. Staff Meet., Mayo Clin.* **12**: 737, 1937.
9. Spear, P. W.: Fibrinous Pericarditis Following Thyroidectomy, *South. M. J.* **31**: 215, 1938.
10. Bing, H. I.: Epidemic Pericarditis, *Acta med. Scandinav.* **80**: 29, 1933.

BILATERAL PULMONARY INFARCTION AND PNEUMOTHORAX
COMPLICATING HYPERTENSIVE, CORONARY HEART
DISEASE WITH MYOCARDIAL INFARCTION:
REPORT OF A CASE

H. MILTON ROGERS, M.D.

ST. PETERSBURG, FLA.

SPONTANEOUS pneumothorax has been reported in association with a number of clinical conditions, including tuberculosis, pneumonia, and bronchial asthma, and secondary to mediastinal emphysema. Marks¹ has observed pneumothorax secondary to pulmonary infarction. According to Hamman,² spontaneous pneumothorax may be produced by any of four mechanisms: (1) rupture of subpleural blebs, (2) a rent in the pleura due to pull of adhesions, (3) rupture into the pleura of congenital pulmonary cysts, or (4) mediastinal emphysema with rupture of the mediastinal pleura. He expressed the opinion that, when bilateral spontaneous pneumothorax is present, mediastinal emphysema must precede the pneumothorax.³

It is the purpose of this paper to report a case of bilateral spontaneous pneumothorax associated with pulmonary infarction and myocardial infarction. Other features of clinical interest in the case were the marked increase of the diastolic blood pressure after renal infarction and the absence of further intracardiac or peripheral manifestations of vascular thrombosis after the institution of dicumarol.

REPORT OF A CASE

The patient was a white man, 44 years of age, examined first Dec. 14, 1944. He complained chiefly of dyspnea and cough. He stated that four weeks previously he had been seized with severe substernal thoracic pain, which extended to the left shoulder and elbow. Morphine was necessary for relief. Part-time rest in bed had been instituted for two weeks. Although dyspnea and cough had made their appearance, he then had been permitted to resume light activity. This had been accompanied by increased shortness of breath and hemoptysis. The twenty-four hours prior to the first examination had been spent on the train, with symptoms increasing in intensity. Nausea and vomiting were present also.

The past history revealed hypertension of ten to twelve years' duration. The blood pressure had ranged from 200/100 to 210/110. There was no history of rheumatic fever, scarlet fever, chorea, or recurrent sore throats.

The results of physical examination revealed a severely dyspneic, cyanotic, acutely ill white man. The pulse rate was 140 beats per minute; the blood pressure was 150/100; the temperature was 100.2° Fahrenheit. There were restricted expansion and posterior dullness to percussion of the right portion of the thorax. Râles were present over the right portion of the thorax anteriorly and posteriorly. A protodiastolic gallop rhythm was present at the apex. No murmurs were heard. The edge of the liver was palpable one fingerbreadth below the costal margin.

Received for publication Oct. 25, 1945.

Examination of the urine revealed specific gravity, 1.021; pH, 4.5; albumin, Grade 2 (on the basis of 1 to 4 in which 1 represents the least and 4 the greatest amount of albumin); sugar, negative; and 2 to 4 leucocytes per high-power field. Erythrocytes numbered 5,090,000, and leucocytes, 17,400 per cubic millimeter of blood. The concentration of hemoglobin was 95 per cent (Sahli). The percentages of the various types of leucocytes were as follows: polymorphonuclears, 73; staff cells, 7; eosinophils, 2; lymphocytes, 15; and monocytes, 3. The electrocardiogram was interpreted as consistent with anterior myocardial infarction (Fig. 1). Roentgenographic examination of the thorax revealed elevation of the right side of the diaphragm. There were mottled shadows throughout the entire right pulmonary field with a large circular shadow of increased density in the region of the right middle lobe (Fig. 2). The left side of the thorax showed extensive mottling throughout. Both costophrenic sinuses were clear. The transverse diameter of the thorax measured 31 cm., and that of the heart was 16 centimeters. The findings were interpreted as being consistent with pulmonary infarction, but bronchopneumonia could not be excluded.

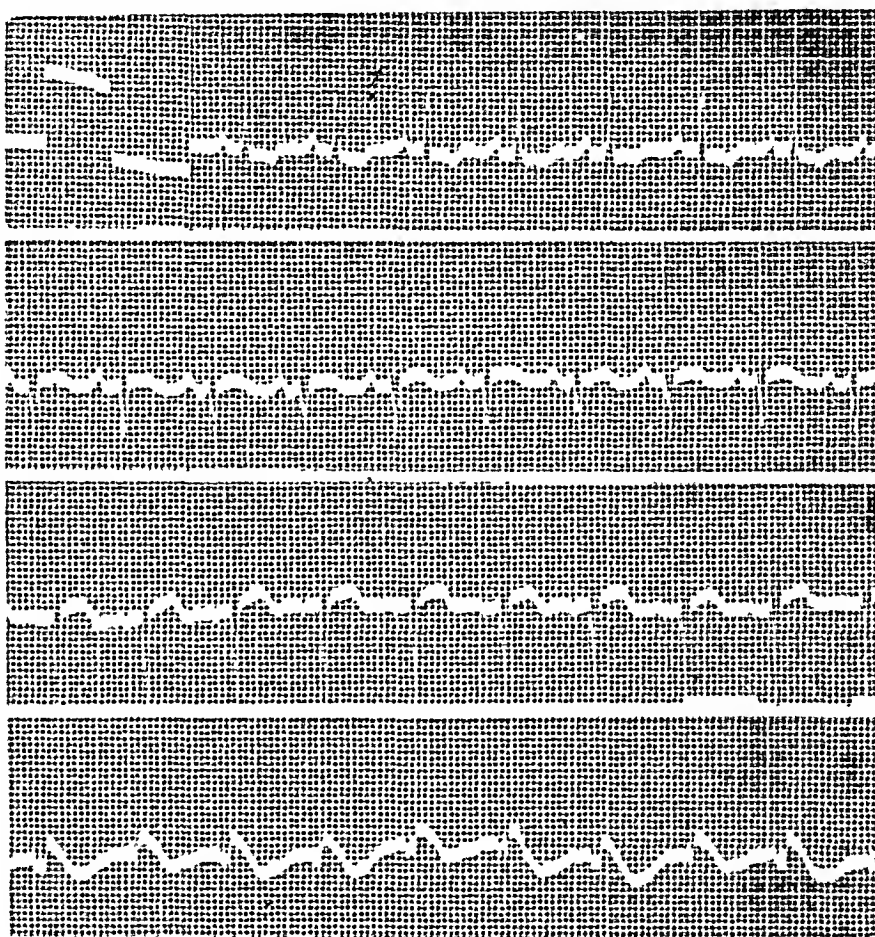


Fig. 1.—Electrocardiogram consistent with anterior myocardial infarction.

Routine measures for treatment of congestive heart failure, including administration of digitalis and complete rest in bed, were begun. Penicillin was likewise administered in view of fever, leucocyte count, and roentgenographic examination. Administration of 15,000 units of penicillin every third hour was continued for seven days. There was improvement of dyspnea and cough, and in three days the temperature had returned to normal. By December 19 the gallop rhythm had disappeared and leucocytes numbered 11,700 per cubic millimeter of blood,

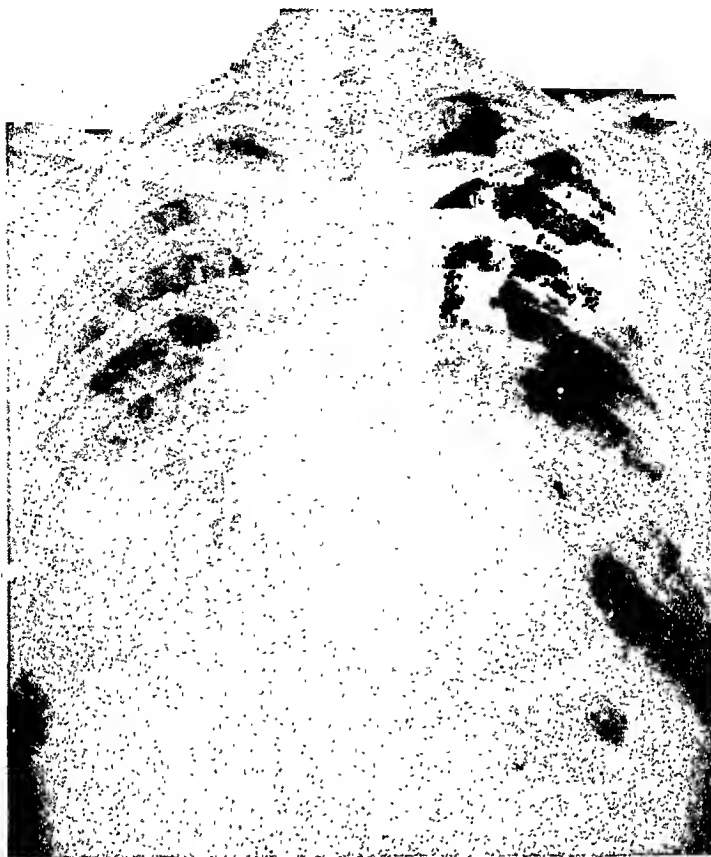


Fig. 2.—Bilateral pulmonary infarcts.



Fig. 3.—Bilateral pneumothorax and bilateral pulmonary infarcts.

with 83 per cent polymorphonuclears. Beginning December 21, however, there was an elevation of temperature for two days to 101 to 102° Fahrenheit. The cough became more severe on December 23 and was accompanied by severe pain in the right side of the thorax without further elevation of temperature. Roentgenographic examination of the thorax now revealed bilateral pneumothorax with severe passive congestion in both pulmonary fields and probable regions of infarction in the inferior lobes (Fig. 3). Since dyspnea was increased as a result of the bilateral spontaneous pneumothorax, oxygen was administered by means of a tent for three days.

There appeared to be gradual improvement until December 30, when there was observed sudden severe pain in the upper right quadrant of the abdomen, extending to the right flank and groin. There was sudden elevation of temperature to 102° F., and leucocytes numbered 25,050 per cubic millimeter of blood, with 89 per cent polymorphonuclears. Analysis of the urine revealed albumin, Grade 4, with many hyaline and granular casts. A diagnosis of infarction of the right kidney, probably secondary to embolization of the right renal artery, was made. The condition of the patient became critical with temperature rising to 102° F. and pulse rate to 150 beats per minute. Protodiastolic gallop rhythm reappeared. There was a transient drop of blood pressure to 140/90, but subsequent determinations revealed pressures ranging from 170/130 to 180/140. Nausea and vomiting reappeared and abdominal distention developed.



Fig. 4.—Clear lung fields.

By Jan. 6, 1945, there was improvement, with disappearance of nausea, vomiting, and abdominal distention. Dyspnea and cough were less troublesome. The temperature returned to normal, and the pulse rate ranged from 90 to 100 beats per minute. Roentgenographic examination of the thorax Jan. 19, 1945, revealed complete resolution of the multiple infarcts and both lungs were fully expanded (Fig. 4). There was a decrease of the size of the heart and considerable decrease of the passive congestion. The condition of the patient at this time had improved to such an extent that he was dismissed from the hospital.

For the next two months the patient was examined at frequent intervals. Administration of digitalis and ammonium chloride, restricted intake of fluid, and limited activity were con-

tinued. The dyspnea and cough did not completely disappear, and toward the end of this period of observation they increased in severity. These symptoms were now accompanied by painful enlargement of the liver, and edema of the ankles appeared for the first time. These manifestations of right heart failure developed rapidly so that the patient was readmitted to the hospital March 14, 1945.

The results of re-examination revealed pulse rate, 100 beats per minute; temperature 98° F.; and blood pressure, 170/140 to 176/150. Protodiastolic gallop rhythm was present. The second sound at the pulmonic area was louder than at the aortic area. No murmurs were present. The liver was palpated for a distance 5 cm. below the right costal margin. Grade 2 edema of the ankles was present.

Complete rest in bed was instituted and the same medication was continued. In view of the previous pulmonary infarctions, dicumarol therapy was instituted, maintaining the prothrombin time (Quick method) between thirty-five and sixty seconds. As nausea was still severe, lanátosid-C was substituted for digitalis. Roentgenographic examination of the thorax revealed passive congestion in both pulmonary fields. The transverse diameter of the heart had increased to 20.5 centimeters. On analysis of the urine the albumin was found to be Grade 4 with 16 to 18 hyaline and 7 to 10 granular casts per high-power field. The concentration of nonprotein nitrogen was 45.5 mg. per 100 c.c. of serum.

Increasing dyspnea developed and administration of mercurphylline injection (mercupurin) was started. Satisfactory diuresis occurred; at times as much as 3,500 to 4,000 c.c. of urine in twenty-four hours was obtained after the intravenous administration of 1 c.c. of mercurphylline. The manifestations of right heart failure continued and pleural effusions developed bilaterally. On April 9, 1945, 2,500 c.c. of amber-colored fluid was obtained by right thoracentesis. Subsequently, thoracentesis was done as follows: April 11, left (1,700 c.c.); April 15, right (2,000 c.c.); April 22, left (1,700 c.c.). There was only slight improvement of symptoms. Death occurred suddenly on April 23, 1945, 130 days after the first examination.

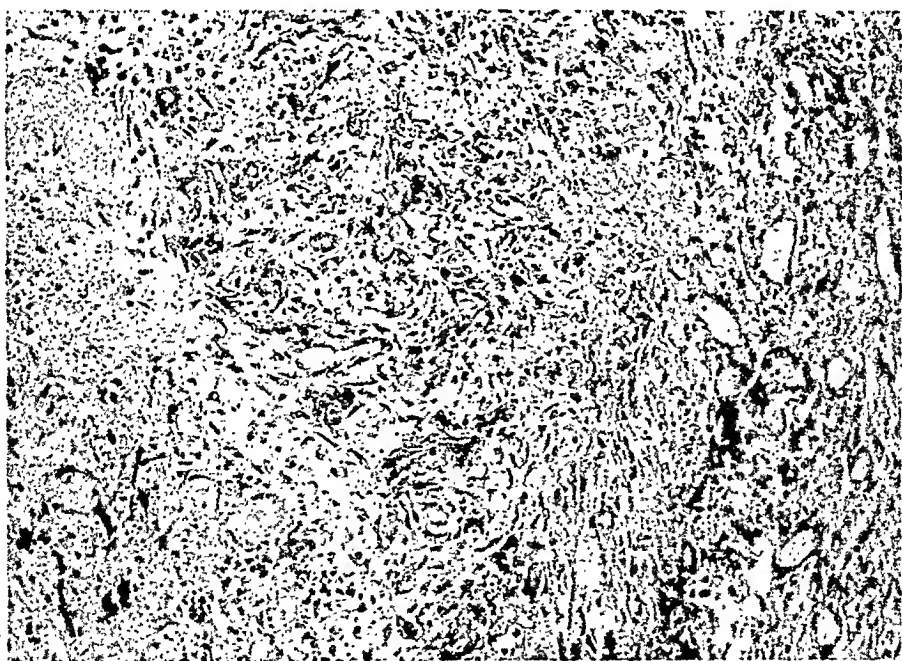


Fig. 5.—Lung at the edge of the infarct with fibroblasts and newly formed capillaries ($\times 125$).

At necropsy the following observations were deemed significant: The heart was moderately enlarged and weighed 600 grams. The right ventricular wall measured 6 mm. and the left ventricular wall measured 20 mm. in thickness. The left ventricular wall in the anterior apical region was thinned to a width of 2 to 3 mm. with formation of an aneurysm. There was an old, well-

organized thrombus in the left ventricle, measuring 6 by 5 by 2 cm. and firmly adherent to the endocardium beneath the aneurysm. Smaller old mural thrombi were present in the right ventricle between the trabeculae carneae. The valves were normal.

The coronary sclerosis of the left circumflex and the right coronary arteries was Grade 2. The sclerosis of the left anterior descending coronary artery was Grade 3 and the artery was occluded by an old ante-mortem thrombus which originated 1.0 cm. from the bifurcation of the left coronary artery.

There was approximately 1,000 c.c. of amber-colored fluid in each pleural cavity. Over the right middle lobe there was a small pleural cyst, measuring 1.5 by 1.0 by 1.0 cm. and containing an organized blood clot. The right lower lobe was atelectatic and contained an organized infarct

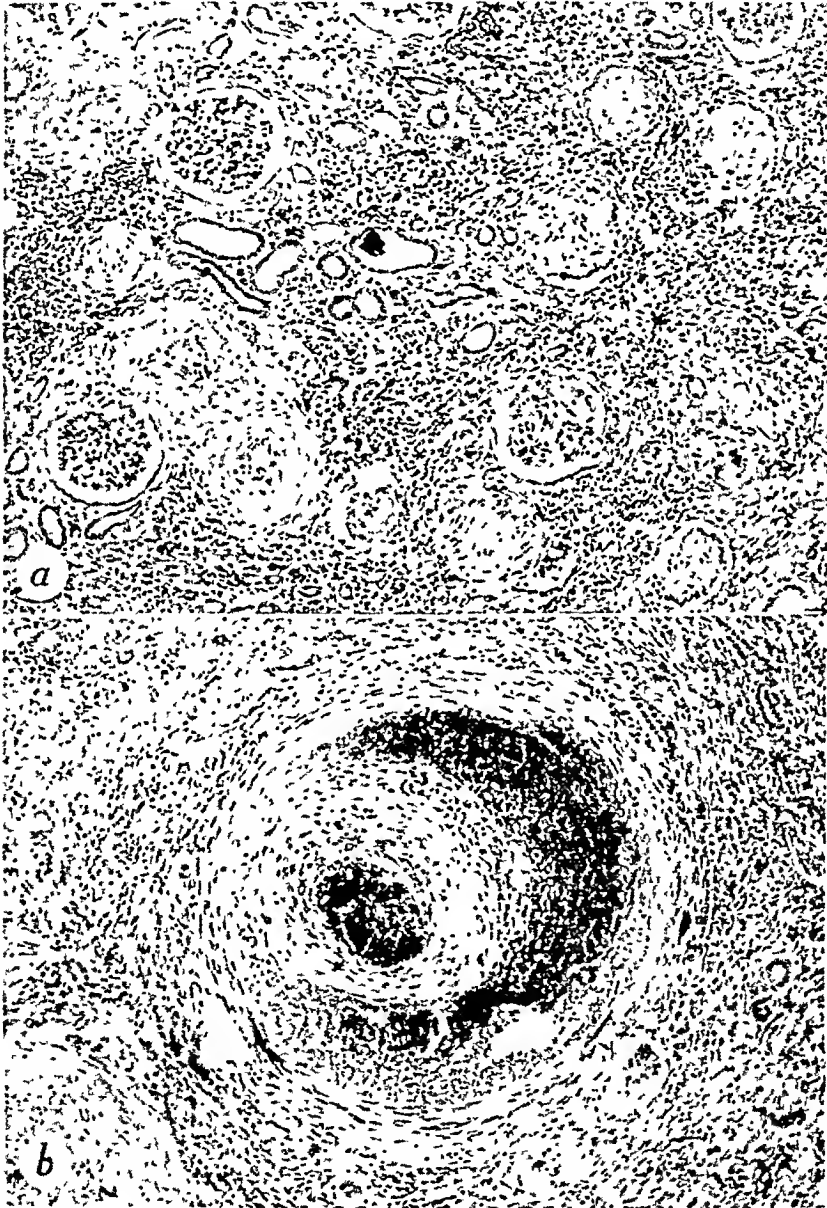


Fig. 6.—Right kidney. *a*, Hyalinized glomeruli, increased interstitial tissue, lymphocytes, and marked medial thickening of small arteries ($\times 90$). *b*, Medium-sized artery with dissecting hemorrhage in the media ($\times 90$).

measuring 4.0 by 4.0 by 3.0 centimeters. Smaller infarcts were present in the right middle lobe and the left lower lobe. There were well-organized thrombi in the pulmonary arteries leading to the right middle and lower lobes and left lower lobe.

In the liver there was the nutmeg appearance of chronic passive congestion.

The right kidney was atrophic and weighed 45 grams. More than three quarters of its parenchyma was destroyed by old and recent infarcts. The left kidney was hypertrophied and weighed 325 grams. The right renal artery was narrowed by atherosclerotic plaques and measured 0.5 cm. in circumference, whereas the left renal artery measured 1.5 cm. in circumference. No thrombi were found in the renal arteries.

Histologic Examination.—In sections of the left ventricle at the site of aneurysm, there was no normal myocardium. Most of the myocardium had been replaced by fibrous connective tissue. A few regions contained old degenerating muscle fibers without nuclei; these fibers were surrounded by fibroblasts. In some regions there were newly formed capillaries. There was a firmly adherent mural thrombus attached to the endocardium.

There was marked atherosclerosis in the left anterior descending coronary artery. The lumen was partially occluded by an old organized thrombus undergoing organization and recanalization. In the center there was a recent ante-mortem thrombus which completely occluded the lumen.

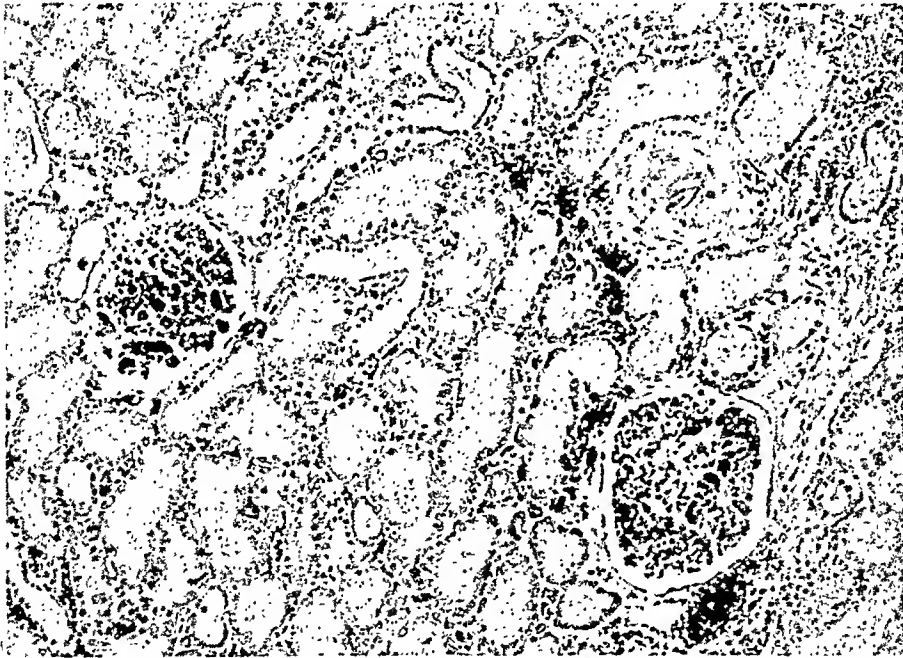


Fig. 7.—Left kidney. Normal glomeruli, tubules, and interstitial tissue with moderate medial thickening of small artery ($\times 90$).

In all sections of the lung the alveoli contained large numbers of pigment-laden macrophages. In some regions the alveoli were also filled with erythrocytes and pink-staining edema fluid. There was medial hypertrophy of the small and medium-sized pulmonary arteries. Small foci of organization were present, and in a few sections overgrowth of the alveolar epithelium was seen. There was squamatization of bronchial epithelium in several sections. In the right middle and lower lobes and left lower lobe old pulmonary infarcts were seen. Organization at the edges of the infarcts was present, as manifested by granulomatous reaction with fibroblasts and newly formed capillaries (Fig. 5). The pleural cyst over the right middle lobe contained ghosts of erythrocytes and fibrin. A granulomatous reaction was present at the edge of the organized blood clot.

In the liver the sinusoids in the region of the central veins were congested and filled with erythrocytes. In the same location foci of necrosis were present.

The sinusoids of the spleen were congested and filled with erythrocytes. There was marked hyalinization of the arterioles.

In the right kidney there were numerous regions of old and recent infarction. In the few remaining regions of renal tissue there was marked atrophy with increase of interstitial tissue, lymphocytes, atrophic tubules, and hyalinized glomeruli (Fig. 6, *a*). Marked medial hypertrophy was present in arteries and arterioles. In one medium-sized artery there was a dissecting hemorrhage into the wall of the media (Fig. 6, *b*).

In sections of the left kidney, the glomeruli, tubules, and interstitial tissue appeared normal. Medial hypertrophy was present but to a lesser degree than that seen in the right kidney (Fig. 7).

The following anatomic diagnoses were made: Hypertrophy of the heart (600 grams); coronary sclerosis Grade 2 to 3 with old thrombosis of the left anterior descending coronary artery; myocardial infarction (old) of the anterior and apical surfaces of the left ventricle with formation of aneurysm; mural thrombi (old) of right and left ventricles; thrombosis (old) of the branches of the pulmonary artery to the right middle and lower lobes and left lower lobe; chronic passive congestion of the liver; arteriosclerotic occlusion of the right renal artery; old and recent infarcts of the right kidney with atrophy.

COMMENT

In the case presented, hypertensive heart disease was followed by coronary thrombosis and occlusion of the left anterior descending coronary artery, with myocardial infarction of the anterior and apical surfaces of the left ventricle. These changes in turn led to ventricular aneurysm and formation of mural thrombi in both ventricles. Embolization of the pulmonary arteries and pulmonary infarction followed. During the period of acute pulmonary infarction, bilateral spontaneous pneumothorax developed. The patient recovered from multiple pulmonary infarction with bilateral spontaneous pneumothorax, but death occurred four months later as a result of right heart failure.

In Marks'¹ discussion of pulmonary infarction and pneumothorax, he emphasized the fact that septic infarcts are more likely to give rise to pneumothorax than are uninfected infarcts and stated that, if necrosis occurs within the infarcted region and pneumothorax results, there is likely to be a rapid outpouring of purulent exudate, thus giving rise to pyopneumothorax. In the first case reported by Marks, thrombi were observed in the right pulmonary artery and small regions of consolidation were present in each lung. No further description of the lung was given. In his second case there was gangrene of the middle and lower lobes of the right lung with empyema. Histologic study of the lungs was not given in either case.

With pulmonary infarction, secondary infection of the infarcted lung is not essential for the production of pneumothorax. In the case reported, the pulmonary infarcts were probably the result of emboli originating from bland mural thrombi present in the right ventricle. The popliteal and femoral veins, however, cannot be entirely eliminated as the source of the emboli. There was no demonstrable evidence of systemic infection, the infarcts were not secondarily infected, and organization was occurring, as manifested by the granulomatous reaction at the edges of the infarcts. The histologic appearance of the pulmonary in-

farcts was consistent with the four-month history, coinciding with the bilateral spontaneous pneumothorax.

It is not possible to state the exact mechanism of formation of spontaneous pneumothorax in this case. It is possible that air may have passed directly into the pleural cavities during the period of pulmonary infarction, as suggested by Marks. It seems more logical, however, that during paroxysms of coughing, rupture of the alveoli of the lung occurred, thereby permitting passage of air into the interstitial connective tissue of the lung. This is in accord with the view of Hamman,² who expressed the opinion that air gaining access to the interstitial tissue of the lung travels along the pulmonary vessels until it reaches the mediastinum. The air, having reached the mediastinum, ruptures through the thin mediastinal wall into the pleural cavity. The bilateral occurrence of spontaneous pneumothorax, however, is evidence in favor of mediastinal emphysema preceding the pneumothorax.³

It has been reported that spontaneous mediastinal emphysema and pneumothorax may be confused with heart disease.⁴ In the case reported, hypertensive heart disease and coronary heart disease with myocardial infarction coexisted with spontaneous bilateral pneumothorax. The presence of pneumothorax superimposed on pulmonary and myocardial infarction not only adds diagnostic difficulties, but also complicates therapeutic measures.

It is possible that the partial occlusion of the right renal artery with atrophy and infarction of the kidney played a role in the causation of the hypertension. The manifestations of vascular disease were more severe in the atrophic than in the hypertrophic kidney. However, it is realized that it is impossible by gross examination or histologic study of the kidneys in cases of unilateral renal disease to state that the atrophic kidney was the cause of hypertension in any specific case.⁵ It was observed clinically, however, in this case that after one episode of renal infarction the diastolic blood pressure was higher than it had been before the episode. This has been recorded previously.^{6,7}

Dicumarol has received much attention in the prevention of intravascular thrombosis. It was used in this case as a prophylactic measure five weeks prior to death, with the hope of preventing any further thrombotic or embolic manifestations. During this period of administration of dicumarol, no embolic phenomena were observed, although congestive heart failure was marked. At post-mortem examination all thrombi observed in the heart and lungs were old and probably had existed prior to the beginning of dicumarol therapy.

SUMMARY

Spontaneous bilateral pneumothorax may occur in association with pulmonary infarction. Secondary infection of a pulmonary infarct is not essential for the development of pneumothorax. In the case reported, pulmonary infarction was probably secondary to ancient myocardial infarction. A rise in the diastolic blood pressure was observed clinically after one episode of renal infarc-

tion. Dicumarol was used prophylactically with the hope of preventing additional intravascular thromboses. Additional thrombotic manifestations were not observed after the administration of dicumarol in this case.

REFERENCES

1. Marks, J. H.: Pulmonary Infarction as a Cause of Pneumothorax, *New England J. Med.* 223: 934, 1940.
2. Hamman, Louis: A Note on the Mechanism of Spontaneous Pneumothorax, *Ann. Int. Med.* 13: 923, 1939.
3. Hamman, Louis: Mediastinal Emphysema. The Frank Billings Lecture, *J. A. M. A.* 128: 1, 1945.
4. Miller, Henry: Spontaneous Mediastinal Emphysema With Pneumothorax Simulating Organic Heart Disease, *Am. J. M. Sc.* 209: 211, 1945.
5. Baggenstoss, A. H., and Barker, N. W.: Unilateral Renal Atrophy Associated With Hypertension, *Arch. Path.* 32: 966, 1941.
6. Prinzmetal, Myron, Hiatt, Nathan, and Tragerman, L. J.: Hypertension in a Patient With Bilateral Renal Infarction; Clinical Confirmation of Experiments in Animals, *J. A. M. A.* 118: 44, 1942.
7. Fishberg, A. M.: Hypertension Due to Renal Embolism, *J. A. M. A.* 119: 551, 1942.

PURPURIC MANIFESTATIONS OF RHEUMATIC FEVER AND ACUTE GLOMERULONEPHRITIS

LIEUTENANT COMMANDER REVERDY H. JONES, JR., M.C., USNR, AND
LIEUTENANT (J.G.) WILLIAM W. MOORE, M.C., USNR
U. S. NAVAL HOSPITAL, PORTSMOUTH, VA.

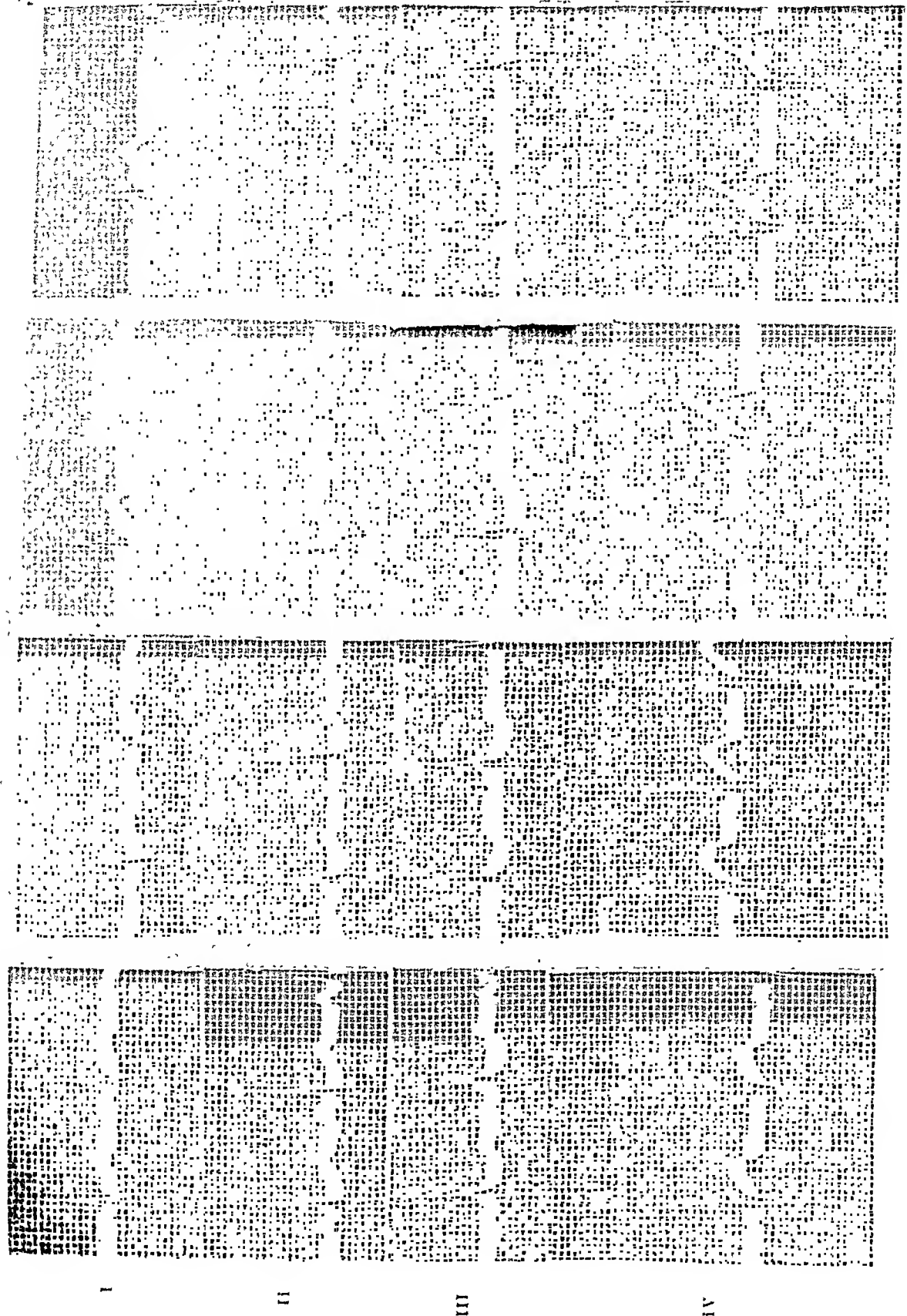
A VARIETY of hemorrhagic conditions, characterized by spontaneous bleeding beneath the skin, from the mucous membranes, or into the joints, have been grouped together under the term "purpura." The subcutaneous hemorrhages appear as small, discrete, purplish spots known as petechiae, or as larger splotchy, confluent areas referred to as ecchymoses. Purpura, like fever, headache, or pain, is only a symptom or manifestation of an underlying pathologic condition which in some cases is very evident but in others assumes an idiopathic nature. The present study is concerned only with simple purpura, without demonstrable blood changes, as noted in two specific conditions. Purpura of this type is a manifestation of many diseases and disorders. In some it results from mechanical causes such as venous stasis or emboli in endocarditis. In others it is due to acute infectious diseases, most notably cerebrospinal meningitis. It is also a consequence of nutritional disorders and the administration of certain drugs, particularly quinine, atropine, and the iodides.

Three cases of symptomatic purpura are presented. In two, the etiology was rheumatic fever, and in the third it was acute glomerulonephritis. The first two cases presented an unusual problem since, due apparently to pure coincidence, they were admitted to the same sick bay within six hours of each other and with nearly identical histories. A thorough search revealed no common toxic agent which might have caused this unusual circumstance. The two men worked in different places at different types of work, slept in entirely separate barracks, and ate at different mess halls. One of these cases became even more interesting when signs of renal disease became so evident that a co-existent diagnosis of both rheumatic fever and acute nephritis seemed justified.

CASE HISTORIES

CASE 1.—W. K., a 23-year-old Motor Machinist's Mate, Second Class, was admitted to the sick list Feb. 7, 1945. Three weeks previously he had had acute tonsillitis which had improved rapidly following the administration of sulfadiazine. Three days prior to admission, he began to have swelling and local heat and pain in the left knee, followed rapidly by migrating polyarthritis. The next day a red rash appeared over both lower legs, and on the day of admission he had a severe chill, followed by fever, palpitation, and generalized malaise. The past, occupational and family histories were negative as concerned rheumatic fever, allergy, or exposure to toxic agents.

Received for publication Dec. 31, 1945.



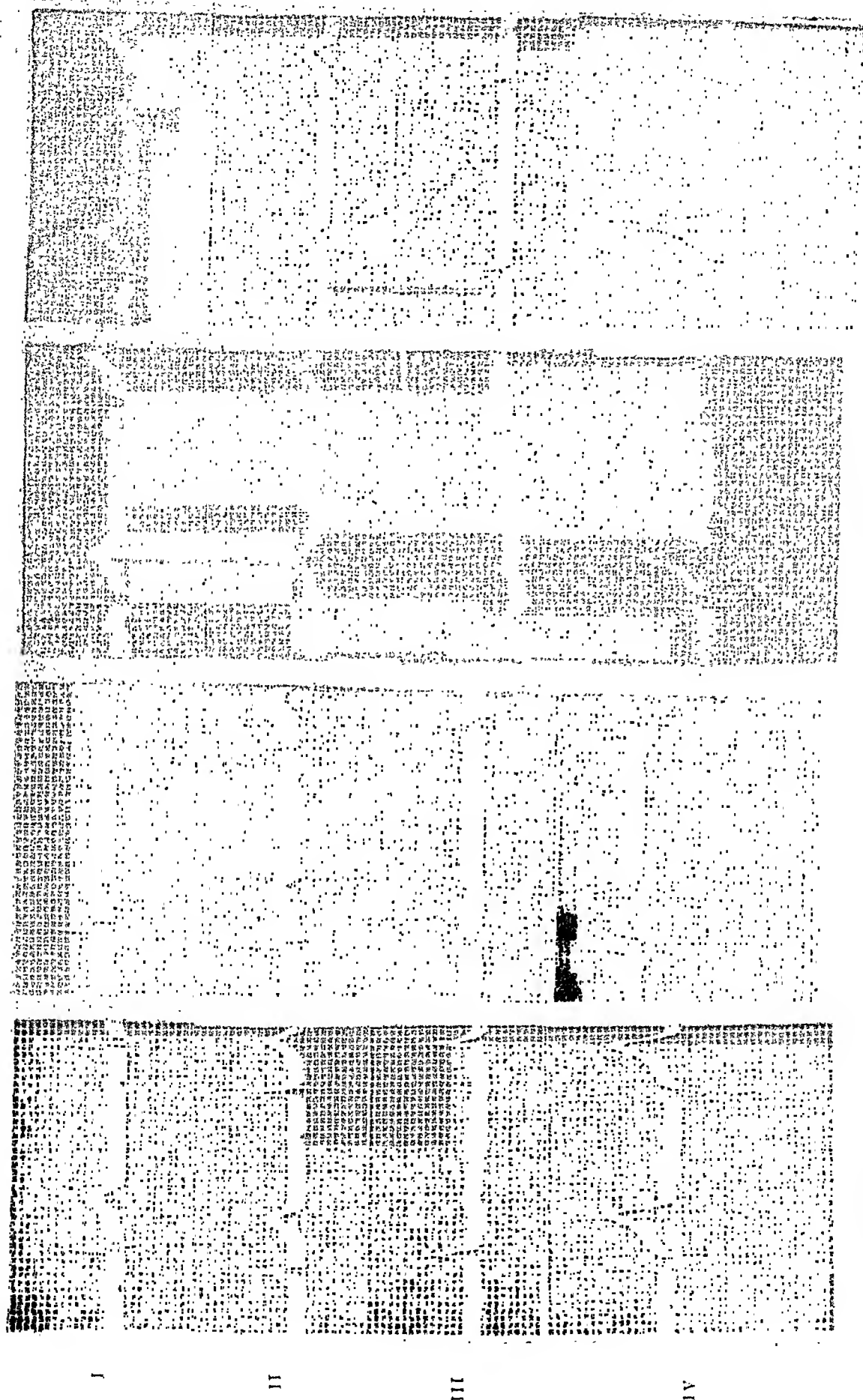
2/8/45
P-R Interval, 0.16

2/10/45
P-R Interval, 0.20

2/11/45
P-R Interval, 0.24

2/12/45
P-R Interval, 0.26

Fig. 1.—Case 1. The P-R intervals progressively lengthened until their duration was 0.26 second. This interval decreased and is seen to be within normal limits in the last two tracings. The S-T segments were slightly depressed in the earlier tracings. They returned to normal in the later tracings. Illustration continued on opposite page.



2/14/45
P-R Interval, 0.24

2/19/45
P-R Interval, 0.20

2/23/45
P-R Interval, 0.16

3/5/45
P-R Interval, 0.16

Fig. 1 (Cont'd).—For legend, see opposite page.

On admission, the patient was acutely ill and had considerable pain. The temperature was 101° F., the pulse rate was 90, and the respirations were 20 per minute. The tonsils were large and chronically infected. The heart was of normal size, with sounds of poor quality, an apical gallop rhythm, and a soft, blowing, apical, systolic murmur which was not transmitted. The right wrist and both knees were swollen, red, and hot. The spleen was not palpable. Over the lower legs there was a macular, reddish, discrete, petechial rash, most dense about the ankles and knees. Initial laboratory studies showed: red blood cells, 3,600,000; a moderate leucocytosis; an elevated sedimentation rate of 26 mm. in one hour; and albumin, white blood cells, red blood cells, and coarse and finely granular casts in the urine. A prothrombin determination, a platelet count, and a blood culture were normal. An electrocardiogram (Fig. 1) taken on admission was normal, but serial electrocardiograms for the next five days revealed progressive increase of the P-R interval from 0.16 second to a maximum duration of 0.26 second on the sixth hospital day. Depression of the S-T segments occurred and was considered to be suggestive of ventricular myocardial damage. An x-ray film of the chest and heart was normal.

The diagnosis of acute rheumatic fever with purpuric manifestations, associated with acute nephritis, was made, and the patient was given sodium salicylate. The prothrombin time determinations, although diminished, remained within normal limits.

Four days after admission the rash had practically disappeared, and after seven days there remained only a faint pinkish-brown discoloration. The temperature and pulse rate became normal within seven days, and the joint symptoms rapidly subsided. The apical systolic murmur persisted but did not increase in intensity, and the heart sounds became normal. Seven days after admission the P-R interval had decreased to 0.24 second; five days later it was normal and remained so during the remainder of hospitalization. The sedimentation rate remained elevated and repeated urinalyses continued to show evidence of acute nephritis.

Six weeks after admission the sedimentation rate and all other studies were normal except urinalysis, which continued to show a trace of albumin. Salicylate therapy was discontinued. Two months after admission the patient was allowed out of bed and during the next month his activities were gradually increased; during this time all studies remained normal.

CASE 2.—J. L., a 19-year-old Seaman, First Class, was admitted to the hospital on Feb. 7, 1945. For one week prior to admission the patient had had a slight cold and sore throat, for which he received no medication. The day prior to admission he noted the onset of a painful swelling of the left knee and ankle, followed rapidly by the same symptoms in the right knee, then by the appearance of a rash about the ankles which spread quickly to cover the entire lower legs. The past, occupational and family histories were negative concerning rheumatic fever, allergy, or exposure to toxic agents.

On admission the patient was acutely ill and had severe joint pains. The temperature was 99° F., the pulse rate was 94, and respirations were 16 per minute. The heart was normal in size, its sounds were normal, and a soft systolic murmur was audible over the pulmonic area. The spleen was not palpable. There was local heat, swelling, pain on motion, and tenderness of the left knee and both ankles. Over both lower legs there was a deep red, macular, splotchy rash, in areas so extensive as to appear confluent (Fig. 2).

Initial laboratory studies revealed: red blood cells, 3,900,000; a slight leucocytosis with a normal differential count; elevation of the sedimentation rate to 25 mm. in one hour; and a prothrombin determination 80 per cent of normal. Urinalysis, a blood culture, and a platelet count were normal.

An electrocardiogram taken on the second hospital day revealed a pronounced sinus arrhythmia with a bradycardia, a varying P-R interval, and ventricular escape. Two days later the electrocardiogram showed no significant change except a decreased nodal irritability. On the fourth hospital day the electrocardiogram returned to normal and remained so throughout hospitalization (Fig. 3). An x-ray film of the lungs and heart was normal.

On the second hospital day the temperature rose to 102° F. and there was an exacerbation of the migratory polyarthritis involving the right elbow and wrist.

A tentative diagnosis of acute rheumatic fever with purpuric manifestations was made, and the patient was placed on sodium salicylate therapy. During this time the results of the pro-

thrombin determinations declined but remained within normal limits. Four days after admission the temperature and pulse were normal, the joint symptoms had disappeared, and the rash had faded considerably. The sedimentation rate remained elevated but all other laboratory procedures were normal. The sedimentation rate became normal five weeks after admission. The patient was then allowed out of bed and salicylate therapy was discontinued. During the next month, all studies remained normal, there were no further symptoms or complaints, and the patient's activities were gradually increased.

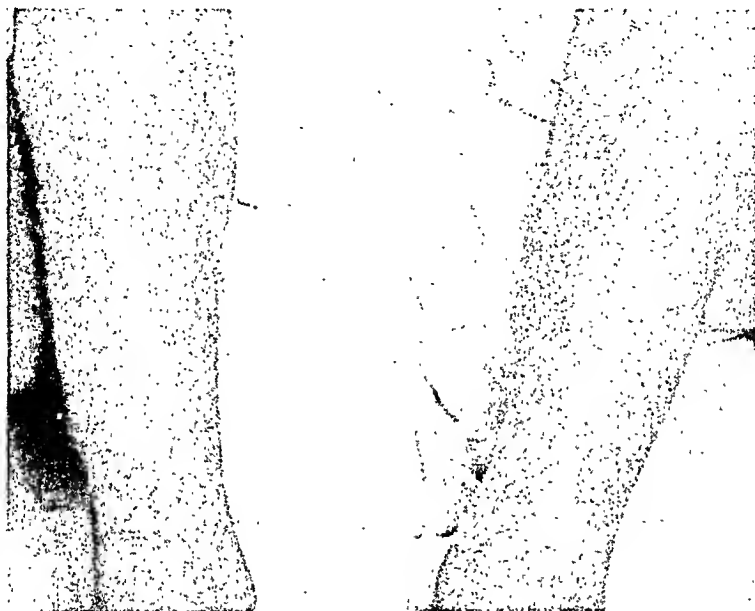


Fig. 2.—Case 2. The rash at the height of the illness was macular in type and deep red in color. It was present over both lower legs and so extensive that it appeared to be confluent.

CASE 3.—F. B., an 18-year-old Seaman, Second Class, was admitted to the hospital on Feb. 25, 1945. Two weeks previously he had had a mild upper respiratory infection for which he was given fifteen sulfadiazine tablets. Two days before admission a rash appeared over both lower legs and spread rapidly during the next thirty-six hours to involve the entire lower extremities. Except for mild soreness associated with the rash, the patient had no complaints. The past, occupational, and family histories were negative for rheumatic fever, allergy, or exposure to toxic agents.

On admission the patient was found to be well developed and well nourished and in no distress. The temperature was 99.8° F., the pulse rate was 100, and the respirations were 20 per minute. The throat appeared normal. No abnormality of the heart was apparent. The spleen was not palpable. Over the lower extremities there was a diffuse, dark, wine-red, macular, mottled rash, in places so extensive as to be confluent (Fig. 4).

Initial laboratory studies revealed: moderate anemia; red blood cells, 3,300,000; slight leucocytosis with a normal differential count; an elevated sedimentation rate of 27 mm. in one hour; a prothrombin determination of 72 per cent of the normal; and a normal platelet count. A blood culture taken on admission was negative. Electrocardiograms on three occasions were normal. Urinalysis revealed only a trace of albumin.

The exanthem rapidly subsided after two days, but the patient continued to have a low-grade fever. Urinalysis showed evidence of nephritis with albumin, red and white blood cells, and casts. The persistent urinary findings were consistent with a clinical diagnosis of acute glomerulonephritis.

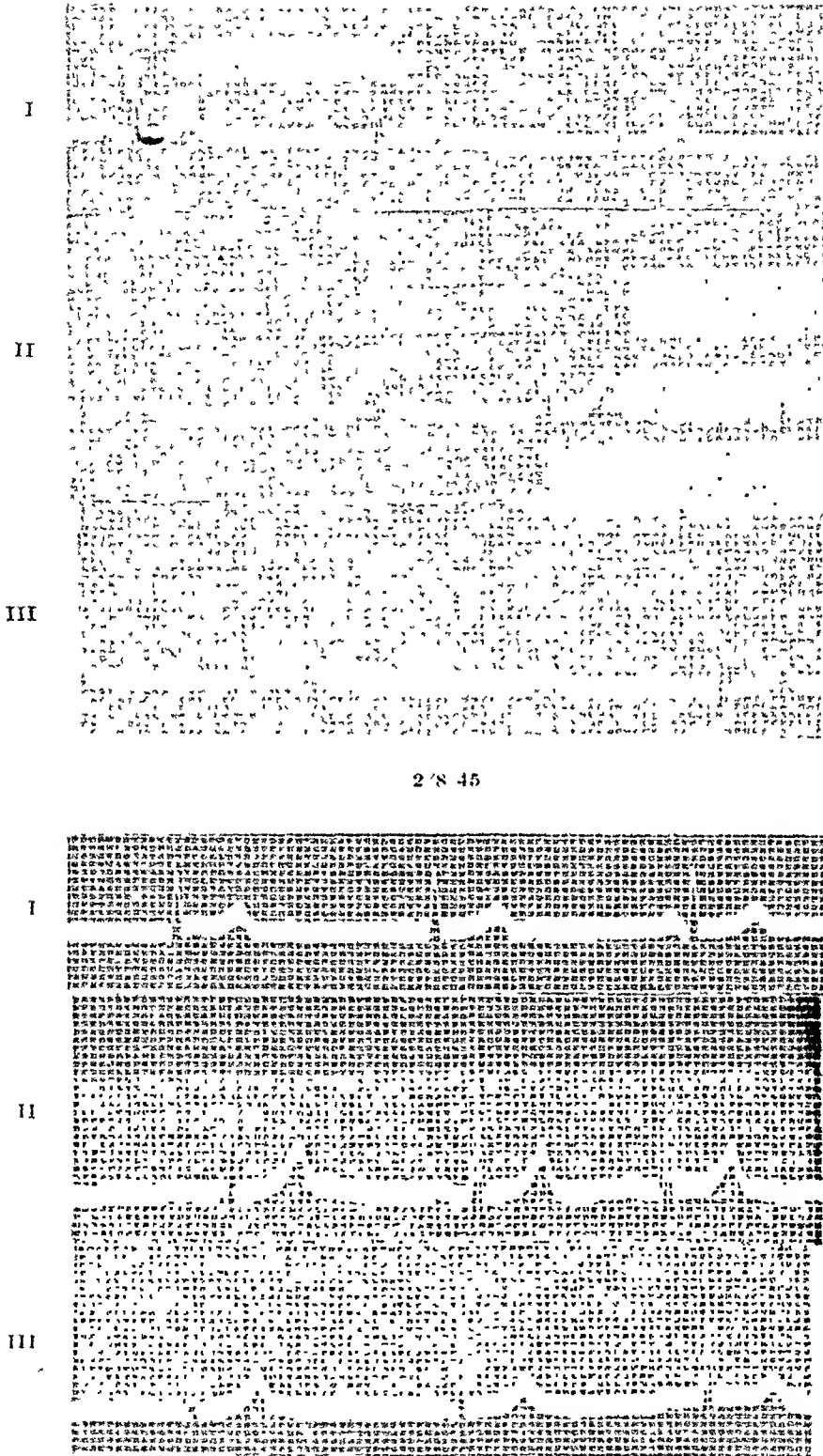


Fig. 3.—Case 2. The electrocardiogram on the second hospital day, Feb. 8, 1945, showed a sinus bradycardia and sinus arrhythmia with ventricular escape. The tracing made Feb. 9, 1945, shows essentially the same findings. Tracings made on and after Feb. 10, 1945, were normal. Illustration continued on opposite page.

I

II

III

2/10/45

3/5/45

Fig. 3 (Cont'd).—For legend, see opposite page.

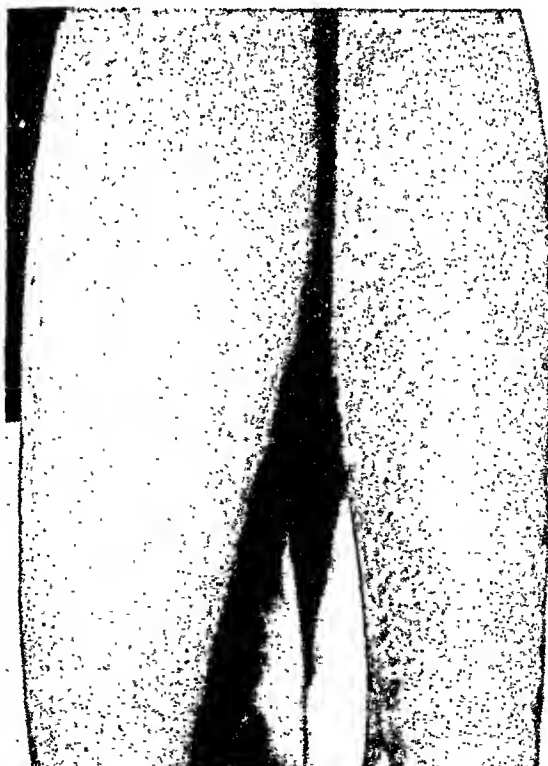


Fig. 4.—Case 3. On admission to the hospital, there was a dark wine-red, macular rash over both lower extremities. The rash was extensive and in places confluent.

On the eighth hospital day the patient began to have transitory pains in both knees and the right elbow of twenty-four hour's duration without any positive physical findings. Otherwise there were no rheumatic manifestations.

Two months after admission the patient had no complaints and physical examination was completely negative, but the sedimentation rate continued elevated and the urinary findings continued to show evidence of nephritis.

DISCUSSION

The clinical association of rheumatic fever with cutaneous nodules and erythematous and hemorrhagic eruptions has been recognized for many years. Wells¹ and then Bright¹ in 1831 recorded instances of an exanthem in rheumatic fever and credit has been given to Rayer² for being the first to describe the association of erythema multiforme with acute rheumatic fever in 1835. Among the more prominent cutaneous manifestations of acute rheumatic fever are the following:

- a. The rheumatic erythemas including erythema multiforme, erythema annulare, and erythema marginatum. Of these, erythema multiforme is by far the most prevalent.
- b. Hemorrhagic eruptions including purpura. This group is distinct from purpura rheumatica or Schönlien's purpura in which the association with rheumatic fever is uncertain.
- c. Subcutaneous nodules.
- d. Erythema nodosum.

Although the estimated incidence of cutaneous manifestations in rheumatic fever has varied from 4 per cent to over 75 per cent, the impression prevails that this condition is infrequent. In a review of rheumatic fever for 1941, Hench³ stated that 5 per cent of the cases demonstrated skin lesions. Keil,⁴ in a summary of 523 cases of acute rheumatic fever, found that 10 per cent had erythematous lesions. Swift⁵ mentions the occurrence of various skin manifestations. White⁶ states that this condition may occur in from 2 per cent to 75 per cent of patients with rheumatic fever, the percentage varying in different groups and in different parts of the world. According to this author erythema multiforme is the commonest of the skin lesions and occurs at some period in 15 per cent of all cases of acute rheumatic fever. In this hospital over the past six months there have been sixty-three admissions for acute rheumatic fever, of which three, or 4.7 per cent, demonstrated cutaneous lesions.

Thus, the general incidence of rheumatic cutaneous lesions is low and the specific appearance of purpura as a skin manifestation is even more rare. Hansen⁷ refers to purpura as being a cause of mistaken diagnosis in only one case in a review of 167 patients with rheumatic fever; and in a further review of 271 cases he mentions purpura as a rare possible source of confusion in the initial diagnosis of rheumatic fever. Both White and Swift refer to purpuric manifestations as occasionally seen. Lichtwitz⁸ mentions purpura as occurring in rheu-

matic fever and considers it a systemic disorder centering in the capillaries which is less severe and distinct from the so-called Henoch's purpura sometimes seen in other infectious conditions.

Purpura, associated with acute glomerular nephritis, appears even more infrequently. Minot¹⁰ mentions purpura as being very rarely associated with chronic nephritis. Fishberg,¹¹ in discussing acute glomerulonephritis, states that purpuric spots occasionally appear in small numbers.

The relationship between acute rheumatic fever and acute nephritis has received extensive study in the past few years. It is felt that generalized involvement of the vascular system is a common accompaniment, if not a constant manifestation, of the rheumatic process. The most common pathologic finding in rheumatic fever has been described as a nonsuppurating, perivascular infiltration, affecting chiefly the smaller vessels, associated with edema and round cell infiltration, and leading to the formation of new connective tissue. Although these changes are most frequently found in the myocardium and endocardium, they have been described as affecting the coronary arteries as well as the renal vessels.

It is well recognized that acute glomerulonephritis in association with acute rheumatic fever is very rare. Hutton and Brown¹² state that in large groups of patients who have acute rheumatic fever, nephritic complications vary from 0.67 to 7 per cent. These authors described four cases of rheumatic fever with clinical evidence of nephritis, in which a typical rheumatic endarteritis, associated with characteristic Aschoff bodies, was demonstrated at autopsy in both the myocardium and kidneys. Blaisdell,¹³ in a review of sixteen autopsied patients with rheumatic fever, found typical perivascular infiltration present in the kidneys in fourteen cases. The primary lesions were in the interstitial tissues and the degenerative hyaline changes observed in the glomeruli were felt to be nutritional disturbances secondary to the interstitial vascular changes. Blaisdell¹³ felt that "while the changes noted are of most frequent occurrence and give rise to a definite interstitial nephritis, the renal damage is only occasionally of sufficient degree to lead to a diagnosis of kidney disease during life."

From the literature it can be accepted that acute rheumatic fever is a disease resulting in widespread pathologic changes. It well may be that the purpuric lesions are themselves a part of this generalized process. Deterioration of the capillary wall, with red blood cells escaping through these capillary defects, is considered to be the underlying cause in this type of purpura. The associated renal lesions and, at rare intervals, the clinical evidence of nephritis, lends further evidence of the generalized nature of the rheumatic infection. It is noteworthy that while acute glomerulonephritis associated with rheumatic fever, even subclinically, is rare, renal lesions of an interstitial nature are observed relatively frequently, although, here again, clinical manifestations are unusual. The high incidence of cardiac involvement and the occasional presence of skin lesions may perhaps be evidence of a similar generalized pathologic process in acute glomerulonephritis. It is of interest and importance that skin lesions or pur-

pura can be an initial symptom of these two maladies, and this fact should emphasize the necessity of searching for the underlying pathogenesis in patients admitted to the hospital with this symptomatic diagnosis.

SUMMARY

1. Three cases of symptomatic purpura have been presented. In two of these the underlying factor was considered to be acute rheumatic fever, in one of which there was evidence of simultaneous nephritis. The primary cause in the third case was acute glomerulonephritis.

2. The various cutaneous manifestations of acute rheumatic fever and acute glomerulonephritis have been outlined.

3. The nephritic manifestations of rheumatic fever have been discussed together with the relationship between these two conditions.

REFERENCES

1. Wells, W. C.; Bright, R.: Quoted by Keil, H.: *Ann. Int. Med.* 11: 2223-2273, 1938.
2. Rayer: Quoted by Keil, H.: *Ann. Int. Med.* 11: 2223-2273, 1938.
3. Hench, P. S., Bauer, W., Ghrist, D., Hall, F., Holbrook, W. P., Key, J. A., and Slocum, H.: The Present Status of Rheumatism and Arthritis, Review of American and English Literature for 1936, *Ann. Int. Med.* 11: 1089-1249, 1938.
4. Keil, H.: The Rheumatic Erythema; A Critical Survey, *Ann. Int. Med.* 11: 2223-2273, 1938.
5. Swift, H. F.: Section on Rheumatic Fever, in Cecil, R. L.: *Textbook of Medicine*, ed. 6, Philadelphia, 1944, W. B. Saunders Company, pp. 99 and 443.
6. White, P. D.: *Heart Disease*, ed. 3, New York, 1944, The Macmillan Co., p. 241.
7. Hansen, A. E.: Staff Meeting Bulletin, Hospital-University of Minnesota, vol. xii, No. 5, November 1, 1940.
8. Hansen, A. E.: Conditions Causing Confusion in the Diagnosis of Rheumatic Fever in Children, *J. A. M. A.* 121: 51, 1943.
9. Lichtwitz, Leopold: *Pathology and Therapy of Rheumatic Fever*, New York, 1944, Grune and Stratton.
10. Minot, G. R.: Section on Purpura, in Cecil R. L.: *Textbook of Medicine*, Philadelphia, 1944, W. B. Saunders Company, pp. 99 and 978.
11. Fishberg, A. M.: *Hypertension in Nephritis*, ed. 4, Philadelphia, 1940, Lea and Febiger.
12. Hutton, R. L., and Brown, C. R.: The Renal Lesion in Rheumatic Fever, *Ann. Int. Med.* 20: 85-98, 1944.
13. Blaisdell, J. L.: The Renal Lesions of Rheumatic Fever, *Am. J. Path.* 10: 287-297, 1934.

Abstracts and Reviews

Herrmann, G. R.: Blood Plasma Proteins in Patients With Heart Failure. *Ann. Int. Med.* 24:893 (May), 1946.

This report is an analysis of blood protein estimations before and after dissipation of the edema in 100 patients with congestive heart failure. The results showed slight but definitely subnormal albumin values with slight compensatory increases in globulin values during the edematous stage. After the dissipation of the edema, the blood proteins did not immediately rise to normal levels, but there were gradual accretions. It is suggested that this lag is due to the fact that the liver cannot assist with protein anabolism until circulatory equilibrium is re-established. The lowest blood protein levels were noted in patients who had suffered congestive failure for many months.

WENDKOS.

Anderson, D. P., Allen, W. J., Barcroft, H., Edholm, O. G., and Manning, G. W.: Circulatory Changes During Fainting and Coma Caused by Oxygen Lack. *J. Physiol.* 104:426 (April), 1946.

Healthy male subjects, aged twenty to thirty years, reclining with the back supported at an angle of about 45 degrees, breathed oxygen-nitrogen mixtures containing approximately 10, 8, 7, and 6 per cent oxygen. The pulse rate, arterial blood pressure, and forearm blood flow (plethysmographic) were recorded. Among thirteen subjects, there were three fainters and ten nonfainters. A typical test in a fainter consisted of an initial rise in pulse rate, systolic arterial pressure, and a slight increase in forearm blood flow followed by vasovagal syncope, during which both the systolic and diastolic pressures and the pulse rate fell below control levels. Nonfainters, however, lost consciousness without showing any signs of the vasovagal reaction and maintained their tachycardia and elevated systolic pressure for the duration of the hypoxic period. In both the fainters and nonfainters forearm blood flow rose to significantly high levels.

In the same group of subjects hypoxia was superimposed upon a simulated hemorrhagic state induced by trapping blood in the lower extremities by means of venous tourniquets. In this "posthemorrhagic" hypoxia a much higher percentage of vasovagal syncope was encountered: ten of the thirteen subjects fainted. The circulatory reactions in this group of experiments were, on the whole, the same as those observed in vasovagal syncope caused by simple hypoxia.

The increase in forearm blood flow in vasovagal syncope and in coma due to hypoxia is considered to be due to vasodilation in skeletal muscle.

It is suggested that wounded men who have lost significant quantities of blood may need oxygen in an atmosphere of low oxygen tension.

FRIEDLAND.

Levy, L., and McKrill, N.: Results in the Treatment of Subacute Bacterial Endocarditis. *Arch. Int. Med.* 77:367 (April), 1946.

These authors present a rather complete review of the literature relating to the therapy of subacute bacterial endocarditis in the past, and record the results of their own treatment in eleven patients. Their plan of treatment consisted of the administration of 200,000 units of penicillin intramuscularly in divided doses every two hours. Sulfadiazine, in a dosage of 1 Gm. every four hours day and night, was also administered with the penicillin. Nine patients received heparin dissolved in 1,000 c.c. of a 5 per cent solution of dextrose in distilled water

as a continuous intravenous drip. The amount of heparin given was that required to maintain a clotting time of between thirty to sixty minutes; in twenty-four hours, this varied between 90 to 300 mg. (9 to 30 c.c.). During heparinization, frequent reactions were observed. These consisted of fever, sometimes with a temperature up to 108° F., chills, mild excitement, and some disorientation. Some of these reactions were believed to be due to the release of protein from the decomposition of bacteria, some to heparin sensitivity, some to embolic phenomena, and some were not explainable. Of the eleven patients, seven were considered to be probably cured; one died from a heparin reaction, and three failed to recover. As a result of autopsy in four cases, they conclude that heparinization favors fragmentation of the vegetation leading to embolism, and that large cerebral hemorrhages are due to bleeding into infarcted areas as a result of the diminished coagulability of the blood. As a result, they advise heparinization only in a few selected cases.

After the patient recovers from an episode of subacute bacterial endocarditis, they suggest frequent follow-up examinations and elimination of foci of infection. BEHL ET.

McIntosh, Berkeley C., and Jackson, Robert L.: Angles of Clearance: A Method for Measuring the Cardiac Size of Children With Rheumatic Heart Disease (A Comparison With the Cardiothoracic Index). Am. J. Dis. Child. 71:357 (April), 1946.

The use of the angle of clearance as a fluoroscopic method for measuring cardiac size was devised by Wilson in 1934. After comparing it with other methods of measuring the size of the heart of patients with rheumatic heart disease, she concluded that the angle of clearance differentiated the normal from the abnormal with greater frequency.

Jackson studied this angle and its reliability as a measurement of cardiac size in 1943 and established normal values for children using a modified technique. The most significant changes were the measurement of two angles instead of one and the designation of these as the first and second angles of clearance. The first angle is that at which the left dorsal border of the heart separates from the transverse process of the vertebrae and the second is that at which the left dorsal border of the heart clears the anterior surface of the vertebral bodies. Wilson had originally established the upper limit of normal for this second angle as 55 degrees. Jackson found the mean value for the first angle to be 51.8 degrees and for the second angle, 63.2 degrees. The standard deviations were 5.8 and 7.4, respectively. Sixty-one patients with inactive rheumatic heart disease and sixteen with active disease are the basis for this report. Comparison was made with the heart sizes obtained by using the cardiac thoracic diameter and physical examination.

Of the entire group of seventy-seven subjects, 68 per cent showed a second angle of clearance above the selected high normal limit of 70 degrees. Forty-one per cent were above the high normal of 57 degrees as measured by the first angle. Thus the second angle of clearance indicated enlargement in a higher percentage of cases than did the first angle. The cardio-thoracic angle was above normal in only 35 per cent of children. However, if the group of children with a considerable degree of enlargement are eliminated, this difference became even greater and in this group the percentages for the two angles are 41 per cent and 12 per cent, respectively. The cardio-thoracic ratio detected enlargement in none of these cases.

The angles of clearance are capable of showing lesser degrees of cardiac enlargement than is the cardio-thoracic diameter and are a valuable adjunct in detecting changes in heart size caused by rheumatic fever. However, the trends of both are parallel in any given subject and both are of value in following an individual subject. HAUB.

Cristie, R. V.: Penicillin in Subacute Bacterial Endocarditis: Report to the Medical Research Council of 147 Patients Treated in 14 Centers Appointed by the Penicillin Clinical Trials Committee. Brit. M. J. 1:381 (March 16), 1946.

This report covers an eighteen-month period. Fifty-five per cent of the patients were "cured," at least for the duration of the four- to eight-month observation period. There were fifty deaths (34 per cent); in the remaining 11 per cent, the final outcome could not be stated with certainty. A streptococcus was the infecting agent in all cases but one; the majority of cases was found to be infected by *Streptococcus viridans*. Penicillin was administered every three hours intramuscularly or as a continuous intramuscular drip with about equal success.

By increasing the period of treatment, using the same total dose (5,000,000 Oxford units), the results improved steadily. With five-day courses, no cures and 70 per cent relapses occurred. Twenty-day courses cured 50 per cent, with a relapse rate of 21 per cent: figures almost twice as high as the percentages obtained with ten-day courses. The best results were obtained with a total dosage of 14,000,000 units in twenty-eight day courses: 61 per cent appeared "cured" during the follow-up period, and no relapses were observed. The duration of treatment was thus the most important factor, but the size of the dose was also important; large doses were more effective. The death rate was relatively constant for each of the groups, ranging between 17 and 40 per cent, with an average of 30 per cent. Relapses usually occurred within thirty days and almost always within fifty days of cessation of therapy. Short, inadequate courses did not prejudice later results with full doses. Although the many relapses were usually early (within a week) the re-treated patients met the averages obtained for the series. Those who did poorly with adequate dosage, though their relapses were longer in appearing, also did poorly when their courses were repeated. A relapse after a twenty-eight day course was serious and justified a six- to eight-week re-treatment period; for the recovery rate was statistically only one-half that of the average obtained for the series. The reason for this was apparently not in the increased resistance of the organism, since this could be demonstrated in only a small minority and was never great. It was concluded that these patients therefore represented a selected group which had a poor response to antibiotic therapy.

In vitro resistance, expressed as multiples of the resistance of the standard Oxford Staphylococcus, was of clinical value only if very great.

Clinical results were as good with "resistant" organisms (compared with the Oxford Staphylococcus) as with "sensitive" strains. Of three patients who had strains more than thirty-two times as resistant as the Oxford Staphylococcus, two died of overwhelming infection. The third patient recovered on a twenty-one day course of 5,000,000 units every twenty-four hours.

Observations on the importance of removing foci of infection and the role of congestive heart failure in the causation of the majority of the deaths were in agreement with reports in current American literature. It was concluded that although excellent results would occur occasionally with any system of dosage lasting for more than ten days, relapses would be unnecessarily frequent unless 5,000,000 units were given for twenty-eight days as routine therapy in all proved cases.

SAYEN.

Jensen, C. R.: Non-Suppurative Post-Streptococcal (Rheumatic) Pneumonitis. Arch. Int. Med. 77:237 (March), 1946.

The author points out that clinical recognition of the pulmonary lesions in rheumatic fever is increasing, but confusion still occurs in the differential diagnosis of this type of pneumonitis. Jensen presents the clinical-pathological findings in a 19-year-old male who died thirty days after the onset of an initial attack of rheumatic fever, featured at first by typical scarlet fever and soon followed by arthritis, nephritis, and pneumonitis. An apparently satisfactory convalescence from scarlet fever was interrupted on the fifteenth day by polyarthritis, dyspnea, hemorrhagic nephritis, and acute hypertension. Under salicylate therapy, the arthritis subsided and the azotemia was reduced. Dyspnea, however, was increased and eventually was accompanied by cyanosis. An electrocardiogram was normal. Râles were audible throughout both lungs. The patient died in great respiratory distress exactly thirty days after the appearance of a streptococcal pharyngitis and fifteen days after the onset of rheumatic pain.

Post-mortem examination showed large lungs, only slightly crepitant, quite solid and plum purple in many areas but not hard and friable. Microscopy revealed monocytic infiltrations in the alveolar walls, consisting of swollen endothelial cells, large mononuclear type lymphocytes, and plasma cells. Some small but dense collections of these cells were noted, but a true Aschoff body was not found. Special stains were negative for organisms. The alveoli contained edema fluid, many erythrocytes, desquamated alveolar cells, monocytes and a generally sparse infiltration of polymorphonuclears.

The kidneys showed focal interstitial hemorrhage and perivascular lymphocytic and plasma cell collections. Many tubules contained blood, but the glomeruli were rather bloodless.

The heart, which was normal grossly, showed small pericardial and also endocardial collections of lymphocytes and plasma cells histologically.

The author emphasizes the unusual opportunity that was presented in this case to study the pulmonary lesions of rheumatic fever uncomplicated by secondary infection or by changes secondary to heart disease. He describes rheumatic pneumonitis as a non-suppurative tissue reaction similar to that seen in other organs following hemolytic streptococcal infection of the upper respiratory tract; in some instances it was so pronounced as to dominate the clinical picture. Jensen points out the possibility of error in diagnosing such a pulmonary involvement as a virus pneumonitis. He recommends more extensive use of the cold pressor and of the antistreptolysin tests in differential diagnosis.

GOULEY.

Hicks, A. M., Painton, J. F., and Hantman, S.: *A Clinical Analysis of Primary Atypical Pneumonia, With a Discussion of the Electrocardiographic Findings.* Ann. Int. Med. 21:775 (May), 1946.

This report is based upon an analysis of 321 cases of atypical pneumonia studied in one of the military hospitals in this country during the recent war. Correlations were established between the incidence of the disease and the age, race, weight, length of service, and the season of the year. The clinical features and laboratory findings were reviewed, and the conclusions reached were found to be similar to those expressed in previous reports concerning atypical pneumonia. The same statement was true of the roentgen patterns and the authors' comments concerning treatment of this disease. Electrocardiographic examinations were employed extensively in sixty-three cases, and twelve of this group showed "electrocardiographic evidence suggestive of myocardial and pericardial involvement." Only two of these patients presented clinical evidence suggestive of cardiac abnormality. The changes consisted of RS-T segment elevations, T-wave inversion, a disturbance of A-V conduction, or combinations of these. In seven of the cases there was electrocardiographic reversal to normal, whereas the other five showed irreversible changes which persisted throughout a three-month period of observation. None of the cases came to autopsy.

WENDKOS.

Blankenhorn, M. A., Vilter, C. F., Scheinker, I. M., and Austin, R. S.: *Beriberi Heart Disease.* J. A. M. A. 131:717 (June 29), 1946.

These authors report their study of a series of twelve cases which were diagnosed as beriberi heart disease from 1940 to 1945. Five patients died in the hospital; autopsies were performed on three patients. The authors believe that the oriental concept of beriberi heart disease as characterized by Wenckebach criteria probably has hindered the diagnosis in many instances. This is particularly true in the large group of cases of beriberi heart disease which do not manifest the rapid circulation and which closely resemble other types of degenerative heart disease. The requirements for diagnosis in their series were (1) insufficient evidence of other etiology; (2) three or more months on a thiamine-deficient diet; (3) signs of neuritis or pellagra; (4) enlarged heart with sinus rhythm; (5) dependent edema; (6) elevated venous pressure; (7) minor electrocardiographic changes; (8) recovery with decrease in heart size; or (9) autopsy findings consistent with beriberi heart disease. The chief factor in diagnosis includes the realization that the etiologic nature of the heart disease is obscure. The differential diagnosis includes coronary arteriosclerosis, Fiedler's myocarditis, and idiopathic hypertrophy.

Alcoholism accounted for the poor dietaries of eleven patients. The majority of diets were deficient not only in thiamine, but also in the other water-soluble vitamins, particularly niacin, riboflavin, and ascorbic acid. Although the time interval required to produce the degree of hypovitaminosis sufficient to produce cardiac abnormalities varies considerably in different individuals, ninety days is the arbitrary point selected. In all twelve cases there was other clinical evidence of nutritive failure. There was always some indication of peripheral neuritis or pellagra. In six cases evidence of both disorders was found. Eight of the twelve patients had anemia, which in three instances was normocytic and in five macrocytic in type. Hypoproteinemia was con-

sistently observed in these patients. Ten of the patients during life showed clinical and roentgenologic evidence of cardiac enlargement. Dependent edema was present in eleven of the twelve patients, and elevated venous pressure was observed in nine. Serial electrocardiograms were made in ten of the twelve cases and all showed abnormalities. The most common abnormalities observed were low voltage and minor alterations in the T waves.

When beriberi heart disease was suspected, the patient was put on a strict regimen which included rest in bed and a diet very low in thiamine. The control period was continued as long as the patient's condition permitted. Large doses of thiamine were then given intravenously. Most cases which showed improvement did so gradually; only one showed dramatic improvement in a period of twenty-four hours. Three of five patients who received digitalis apparently benefited from this drug. There is some uncertainty as to the origin of the dictum that digitalis is of no aid in this condition and that if the heart responds well to this drug the diagnosis of beriberi is eliminated.

While alterations in the myocardium in beriberi heart disease have been described and studied repeatedly for many decades, no pathognomonic picture has been revealed. Three of their cases which came to necropsy showed degenerative changes of the heart muscle and interstitial edema. These observations were considered consistent with but not diagnostic of beriberi heart disease. In two instances in which the nervous system was examined, definite lesions in the central, peripheral, and autonomic nervous systems were revealed. BELLET.

Nathanson, M. H.: Hyperactive Cardioinhibitory Carotid Sinus Reflex. Arch. Int. Med. 77:491 (May), 1946.

This report was based on a study of 115 patients showing hyperactive carotid sinus reflexes. The carotid sinus was considered hyperactive when it fulfilled the following criteria: (1) a cardiac standstill of at least five seconds; (2) cardiac inhibition induced by simple pressure on the carotid sinus without massage of sinus; (3) standstill of equal intensity elicited on several tests. The youngest patient was 30 and the oldest in the group was 81 years of age; the average age was 58.9 years. Of the 115 patients, seventy-seven (67 per cent) presented no symptoms suggestive of carotid sinus syndrome. In ten cases, manifestations of the carotid sinus syndrome were the chief complaints. Attacks of syncope were experienced by only six patients. Symptoms resembling those of carotid sinus syndrome were presented by fifteen patients, but some mechanism other than the hyperactive carotid sinus reflex could be demonstrated as a basis for the attacks. In five of these patients, there was a true vertigo with nausea and tinnitus, indicative of Ménière's syndrome. The sensations following pressure on the carotid sinus had no similarity to the sensations at the time of the spontaneous attacks. In four patients, the symptoms of faintness and dizziness were associated with attacks of paroxysmal tachycardia.

A definite distinction is made between the hyperactive carotid sinus reflex which designated a hyperactive response to stimulation of the carotid sinus and the carotid sinus syndrome which designated a clinical condition. The author explains the presence of symptoms in some and the absence of symptoms in others with similar degrees of sensitivity to a difference in individual response to cerebral ischemia.

This author also made an attempt to determine the site of the hyperactive cardioinhibitory reflex. Pressure over the carotid sinus was shown by Hering to elicit two independent effects: (1) a cardioinhibitory effect and (2) a vasodepressor effect. The former may be abolished by atropine, permitting observations of the vasodepressor effect. Blood pressure readings were taken during stimulation of the carotid sinus, before and after administration of atropine. It was observed that there was definite lowering of the blood pressure following carotid sinus stimulation in the atropinized patient. He therefore concludes that either the vagus center in the medulla or some portion of the efferent path in the vagus nerve must be considered responsible for the hyperactive response. This observation is of practical importance because denervation of the carotid sinus would not insure a consistent and permanent cure if the hypersensitivity was predominantly in the vagus nerve. BELLET.

American Heart Association, Inc.

1790 BROADWAY AT 58TH STREET, NEW YORK, N. Y.

DR. ROY W. SCOTT
President

DR. HOWARD F. WEST
Vice-President

DR. GEORGE R. HERRMANN
Treasurer

DR. HOWARD B. SPRAGUE
Secretary

BOARD OF DIRECTORS

DR. EDGAR V. ALLEN Rochester, Minn.
DR. GRAHAM ASHER Kansas City, Mo.
*DR. ARLIE R. BARNES Rochester, Minn.
DR. ALFRED BLALOCK Baltimore
*DR. WILLIAM H. BUNN Youngstown, Ohio
DR. CLARENCE DE LA CHAPELLE New York City
*DR. TINSLEY R. HARRISON Dallas
DR. GEORGE R. HERRMANN Galveston
DR. T. DUCKETT JONES Boston
DR. LOUIS N. KATZ Chicago
DR. SAMUEL A. LEVINE Boston
DR. GILBERT MARQUARDT Chicago
*DR. H. M. MARVIN New Haven
*DR. EDWIN P. MAYNARD, JR. Brooklyn
*DR. THOMAS M. McMILLAN Philadelphia
DR. JONATHAN MEAKINS Montreal, Can.
DR. E. STERLING NICHOL Miami

DR. HAROLD E. B. PARDEE New York City
DR. WILLIAM B. PORTER Richmond, Va.
*DR. DAVID D. RUTSTEIN New York City
*DR. JOHN J. SANFSON San Francisco
DR. ROY W. SCOTT Cleveland
*DR. HOWARD B. SPRAGUE Boston
DR. GEORGE F. STRONG Vancouver, B. C., Can.
DR. WILLIAM D. STROUD Philadelphia
DR. HOMER F. SWIFT New York City
DR. WILLIAM P. THOMPSON Los Angeles
DR. HARRY E. UNGERLEIDER New York City
*DR. HOWARD F. WEST Los Angeles
DR. PAUL D. WHITE Boston
DR. FRANK N. WILSON Ann Arbor
*DR. IRVING S. WRIGHT New York City
DR. WALLACE M. YATER Washington, D. C.

*Executive Committee.

DR. H. M. MARVIN, *Acting Executive Secretary*

ANNA S. WRIGHT, *Office Secretary*

Telephone, Circle 5-8000

THE American Heart Association is the only national organization devoted to educational work relating to diseases of the heart. Its activities are under the control and guidance of a Board of Directors composed of thirty-three eminent physicians who represent every portion of the country.

A central office is maintained for the coordination and distribution of important information. From it there issues a steady stream of books, pamphlets, charts, films, lantern slides, and similar educational material concerned with the recognition, prevention, or treatment of diseases of the heart, which are now the leading cause of death in the United States. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning the circulation of blood and lymph. Any physician or investigator may become a member of the section after election to the American Heart Association and payment of dues to that organization.

The income from membership and donations provides the sole financial support of the Association. Lack of adequate funds seriously hampers more intensive educational activity and the support of important investigative work.

Annual membership is \$5.00. Journal membership at \$11.00 includes a year's subscription to the AMERICAN HEART JOURNAL (January-December) and annual membership in the Association. The Journal alone is \$10.00 per year.

The Association earnestly solicits your support and suggestions for its work. Membership application blanks will be sent on request. Donations will be gratefully received and promptly acknowledged.

American Heart Journal

VOL. 32

NOVEMBER, 1946

No. 5

Original Communications

RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE IN THE NORTH AFRICAN AND MEDITERRANEAN THEATER OF OPERATIONS, UNITED STATES ARMY

LIEUTENANT COLONEL EDWARD F. BLAND
MEDICAL CORPS, ARMY OF THE UNITED STATES

INTRODUCTORY REMARKS

THE present study was undertaken on behalf of the Surgeon, Mediterranean Theater of Operations, United States Army, to determine the incidence of rheumatic fever and of rheumatic heart disease in Army personnel in this Theater, to observe the effect of wartime conditions upon their clinical course, to appraise the policies adopted for their management, and, finally, to scrutinize the measures now in force for the exclusion of susceptible individuals from overseas assignment. The material upon which this report is based consists essentially of both combat and service troops of the United States Army involved in this Theater from the original landings in North Africa in November, 1942, through the Tunisian, Sicilian, and Italian campaigns to the end of hostilities in May, 1945.

Two factors largely determined the method of approach adopted in assembling the data. First, in view of the now well-recognized chronic nature of rheumatic fever and the disabling effects of valvular heart disease developing therefrom, hospitalization and disposition of these patients overseas were essentially functions of the general hospitals. Second, approximately 95 per cent of the patients involved either were boarded for the Zone of the Interior (the United States) or for limited service, and copies of the board proceedings containing pertinent clinical data were retained by the hospitals and were available for review. Therefore, a study of the clinical records and of the board proceedings of the general hospitals is the basis for the greater part of the factual data recorded herein.

Received for publication March 23, 1946.

METHOD OF INVESTIGATION

During the two and one-half years covered by this report, seventeen general hospitals functioned in this Theater. At the time the final data were assembled, six of these hospitals had been transferred to France and information concerning their experience with rheumatic fever and rheumatic heart disease before leaving this Theater was obtained from the chief of the medical service of each by letter. In another instance (the 26th General Hospital), all records covering their sojourn in North Africa were destroyed by enemy action, but data on the Italian campaign were obtained from them through the chief of the medical service. The remaining ten general hospitals in operation in Italy were visited by me and their records were reviewed. In this fashion complete historical and clinical data were obtained on 841 individuals with rheumatic fever and/or rheumatic heart disease. This group of personally reviewed cases comprises the most valuable source of information in the study and serves as an index of the clinical features of the disease as it occurred in the United States Army in North Africa and Italy.

Next in importance is a smaller series of 100 patients included in the aforementioned group which I, in anticipation of a separate clinical report in collaboration with Captain Marlow B. Harrison, Medical Corps, studied at the 6th General Hospital. In this group we were especially interested in the antecedent history in regard to previous knowledge of heart disease from examinations at school, for insurance, for industrial employment, or for entrance into other branches of the service previous to their final acceptance by the Army, as well as their later experiences in medical establishments after entry into the service. This carefully questioned group, relative small though it is, serves as our principal check on the efficiency and thoroughness of induction examinations.

An additional source of data with reference to the incidence of asymptomatic and unsuspected rheumatic heart disease has been the records of the three medical laboratories to which protocols, as well as sections of tissue of all post-mortem examinations in this Theater, were sent for review and confirmation. Thus the records of the 2nd Medical Laboratory and of the 15th Medical General Laboratory have been studied, and from the 4th Medical Laboratory now in France pertinent data were received by letter. In this fashion 1,507 consecutive post-mortem examinations were available for our purpose.

To supplement this factual data, conferences were held with numerous individuals especially interested or experienced in this field at the headquarters of the Mediterranean Theater of Operations and of the 5th Army, and in the general, station, evacuation, and convalescent hospitals. As a result of these discussions there was agreement that rheumatic fever had been relatively infrequent, that rheumatic heart disease in the majority clearly antedated entry into the service, and, finally, that by limiting this survey to the general hospital, fully 95 per cent of patients with these conditions would be included. The remaining 5 per cent (estimated) would include the occasional patient who, contrary to the established policy in the Theater, was not referred to a general hos-

pital for appraisal, as well as a relatively small number of patients sent directly to the Zone of Interior by station or evacuation hospitals functioning temporarily in the role of a general hospital in newly occupied ports prior to the arrival of the latter. This was the case with the 8th Evacuation Hospital in Casablanca before the arrival of the 6th General Hospital, and, in like manner, of the 7th Station Hospital in Oran and the 52nd and 118th Station Hospitals in Naples. It is our belief, however, that the number of cases escaping attention in this fashion is negligible.

INCIDENCE

Clinical Data.—The over-all clinical data as to incidence assembled from the general hospitals for the two and one-half year period from November, 1942, to May, 1945, is summarized in Table I. In analyzing Table I, it should be remembered that in the process of evacuation a single patient may have been

TABLE I. INCIDENCE AND DISPOSITION OF RHEUMATIC FEVER AND/OR RHEUMATIC HEART DISEASE IN THE GENERAL HOSPITALS IN THE MEDITERRANEAN THEATER OF OPERATIONS, UNITED STATES ARMY (NOVEMBER, 1942, TO MAY, 1945)

GENERAL HOSPITALS	TOTAL CASES	DISPOSITIONS		
		ZONE OF INTERIOR	LIMITED SERVICE	DUTY
3rd*				
6th	183	169 (92.3%)	8 (4.3%)	6 (3.4%)
12th	178	135 (75.8%)	15 (8.5%)	28 (15.7%)
17th	96	91 (94.8%)	2 (2.1%)	3 (3.1%)
21st	85	72 (85.5%)	11 (13.0%)	2 (1.5%)
23rd*				
24th	40	28 (70.0%)	7 (17.5%)	5 (12.5%)
26th†	44	33 (75.0%)	0	11 (25.0%)
33rd	70	59 (84.3%)	7 (10.0%)	4 (5.7%)
36th	49	46 (93.8%)	0	3 (6.2%)
37th	34	23 (67.6%)	7 (20.6%)	4 (11.8%)
43rd	58	56 (96.5%)	2 (3.5%)	0
45th	134	134 (100.0%)	0	0
46th	58	56 (96.6%)	1 (1.7%)	1 (1.7%)
64th	30	29 (96.6%)	1 (3.4%)	0
70th	109	95 (87.1%)	8 (7.3%)	6 (5.6%)
300th	33	27 (81.8%)	4 (12.1%)	2 (6.1%)
Total	1,201	1,053 (87.6%)	73 (6.1%)	75 (6.3%)

*Information requested but not received at time of submission.

†Includes Italy only (see text).

hospitalized in more than one institution; hence, there is an estimated 10 per cent reduplication in these figures, which, however, it was possible to correct in the personally reviewed series of 841 cases which forms the basis of the clinical discussion later. The reduplication noted accounts in part for the disproportionately large number of cases from the 6th, 12th, and 45th General Hospitals, located, as they were, in or near ports of embarkation. An additional factor in connection with these three hospitals was their relatively early arrival and long

sojourn in the Theater. With due consideration for the various modifying factors in the available statistics, there were approximately 1,400 patients in the Mediterranean Theater of Operations with rheumatic fever and/or rheumatic heart disease.

Post-Mortem Data.—The post-mortem material available for study in this connection consists of protocols of 1,507 consecutive autopsies from the records of the 15th Medical General Laboratory and from the 2nd and the 4th Medical Laboratories. Reference has been made to these records in an attempt to arrive at some general idea of the incidence of presumably unsuspected rheumatic heart disease in the Army. As one might expect, the apparent incidence from these figures is low because they are weighted by the fact that most patients in whom valvular heart disease is discovered incidentally during hospitalization for other diseases or injuries are returned to the Zone of the Interior. However, in this series of 1,507 examined patients, there were fifteen instances of rheumatic heart disease in Army personnel, an incidence of 9.9 per 1,000. In thirteen of these fifteen, all of whom died of conditions unrelated to the heart, there were old well-healed lesions of mild degree, involving the aortic valve in two and the mitral valve in eleven. The remaining two patients had active rheumatic carditis. One of these is of considerable interest. This patient, 20 years of age, had pneumonia complicated by a lung abscess. During the course of the illness he developed acute migratory polyarthritides typical of rheumatic fever, a persistent tachycardia, and a loud apical systolic murmur which appeared while he was under observation. In the course of the illness he received five transfusions of whole blood. Following the last transfusion he developed icterus, anuria, and azotemia and died of renal failure. At post-mortem examination the heart weighed 350 grams. The endocardium of the mitral valve showed hemorrhagic areas and small linear verrucous vegetations along the line of closure typical of acute rheumatic endocarditis. Sections of the myocardium also revealed a widespread acute process with edema of the interstitial tissue, mild cloudy swelling of the muscle fibers, areas of hyperemia, and multiple small hemorrhagic foci. Sections of the mitral leaflet showed recent hemorrhagic infiltration together with diffuse infiltration by lymphocytes, plasma cells, and other mononuclear cells. No bacterial organisms were present in the vegetations. This case represents an initial acute attack of rheumatic fever complicating lung sepsis and a fatal transfusion reaction.

In connection with the post-mortem incidence of 0.9 per cent noted in this series, although the figures are not strictly comparable, it is interesting that Clawson reported an incidence of 2.8 per cent for rheumatic heart disease in 30,265 autopsies in Minnesota¹ and that Scott and Garvin in Cleveland found 1.7 per cent in 6,548 autopsies.²

Discussion.—Since rheumatic fever was included among the reportable diseases in this Theater, it is of some interest in the light of this survey to compare our findings with the number of cases formally reported to the Department of Preventable Diseases. It should be noted that our figures discussed in the

foregoing include both active rheumatic fever and "inactive" rheumatic heart disease. However, from the clinically studied group, it will be seen later that 58 per cent of the total number of patients had recognizable rheumatic activity. This indicates that perhaps 600 or more patients of our composite group had rheumatic fever.

For comparison with this figure, we consulted the records of the Surgeon's Office, Mediterranean Theater of Operations, United States Army,* for the actual number of cases reported. This information was available for the twenty-eight months from January, 1943, through April, 1945, and is shown in Table II. The total of 361 cases indicates, in the light of our study, that approximately one-half of the cases of rheumatic fever were formally reported as such. It is of some further interest that only one death is recorded from rheumatic heart disease and one from subacute bacterial endocarditis. We suspect these mortality data are approximately correct.

TABLE II. RHEUMATIC FEVER REPORTED IN THE MEDITERRANEAN THEATER OF OPERATIONS, UNITED STATES ARMY (JANUARY, 1943, THROUGH APRIL, 1945)

YEAR	JAN.	FEB.	MAR.	APRIL	MAY	JUNE	JULY	AUG.	SEPT.	OCT.	NOV.	DEC.	TOTAL CASES
1943	6	7	1	7	2	2	9	8	10	10	13	14	89
1944	11	11	20	2	26	18	22	24	18	21	16	22	211
1945	13	13	19	16									61
Total													361

Perhaps the most important single factor in the relatively low incidence of rheumatic fever in this Theater has been the absence in epidemic proportions of streptococcal sore throats and upper respiratory infections in general among the troops in this area. According to the records of the Surgeon's Office, even minor outbreaks of such were much less frequent than would be anticipated in a comparable civilian population.

It is of some interest to compare these figures on incidence with those available for the overseas forces in World War I (1917-1918). Tables III and IV have been compiled from information contained in *The Medical Department of the United States Army in the World War*³ from the section on Admissions in Europe of White Enlisted Men From April 1, 1917, Through December 31, 1919. It is to be remembered that the number of troops upon which these figures are based probably far exceeded the number involved in the Mediterranean Theater of Operations. Furthermore, the accuracy with which the diagnoses of rheumatic fever and of valvular heart disease were made twenty-five years ago was considerably less than at present. It is reasonable to suspect that many cases of

*We are indebted to Colonel W. S. Stone, Department of Preventive Medicine, for this information.

other now well-recognized types of arthritis and allied conditions were included along with rheumatic fever in the group labelled "acute articular rheumatism." Also, the high incidence of "mitral insufficiency" as shown in Table III suggests that the significance of systolic murmurs at the cardiac apex was overemphasized. In spite of these and other equally obvious discrepancies, the striking disproportion in incidence of these conditions in World War I as compared with this sample of incidence in World War II speaks well for the thoroughness with which subjects with rheumatic fever and those with long-standing valvular disease have been excluded from the overseas forces.

TABLE III. ADMISSIONS IN EUROPE OF WHITE ENLISTED MEN
(APRIL 1, 1917, TO DEC. 31, 1919) (ABSOLUTE NUMBERS)

Acute articular rheumatism	5,745
Valvular diseases of the heart	2,122
1. Aortic insufficiency	144
2. Aortic stenosis	28
3. Mitral insufficiency	1,418
4. Mitral stenosis	241
5. Combined lesions, mitral and aortic	44
6. Tricuspid lesions	3
7. Valvular lesions, unclassified	244
Total admissions (Medical diseases)	702,780

TABLE IV. DEATHS IN EUROPE OF WHITE ENLISTED MEN
(APRIL 1, 1917, TO DEC. 31, 1919) (ABSOLUTE NUMBERS)

Acute articular rheumatism	19
Valvular disease of the heart	50
Total deaths (Medical diseases)	29,272

CLINICAL FEATURES

The data which form the basis of the following observations consist of the group of 841 patients whose hospital records and board proceedings were personally reviewed. This represents more than one-half of the total number of known cases in the Theater and hence serves as a reliable index of the main features of rheumatic fever and rheumatic heart disease under wartime conditions in this part of the world.

These cases fall into two main groups (Table V): I, those patients with active rheumatic fever and, II, those with the physical signs of valvular heart disease (rheumatic type) but without demonstrable rheumatic infection.

Active Rheumatic Fever.—There were 488 patients, 58 per cent of the series with clinical or laboratory evidence of active rheumatic fever. In one-half (246 patients) it represented a recurrence or reactivation of previously known

TABLE V. INCIDENCE OF RHEUMATIC FEVER AND OF RHEUMATIC HEART DISEASE
(841 CASES PERSONALLY REVIEWED)

I	Active rheumatic fever		488 cases (58.0%)
	(a) Rheumatic heart disease	247 (50.6%)	
	(b) Potential rheumatic heart disease	241 (49.4%)	
II	Rheumatic heart disease (Inactive)		353 cases (42.0%)
	Total rheumatic heart disease		600 cases (71.3%)

infection. In the remainder (242 patients) the present illness appeared to be the initial onset of rheumatic infection in so far as could be determined from the history and from the degree of valvular disease present in those with this complication. The presence of well-marked mitral stenosis, for example, was considered evidence of past rheumatic fever, even though there was no suggestion of such in the history. In this group of 242 patients whose illness originated overseas, no clues were apparent to foretell their rheumatic susceptibility. In view of this it was of some interest to inquire into the immediate circumstances which may have been a factor in initiating the illness. In civilian experience it has been repeatedly shown that by far the most frequent event occurring just before, or concurrently with, the onset of rheumatic fever is streptococcal infection of the upper respiratory tract. Occasionally, however, other episodes, nonspecific in character, may apparently act in a similar fashion, especially in regard to recrudescences of the disease. In this connection and limiting the observations to the group of 242 patients with "primary" rheumatic fever, it is noteworthy that the following events occurred with sufficiently striking relationship to the onset to have been recorded in the routine histories of eighty-eight patients; namely, sore throat (sixty-five instances), injury (ten), severe exposure (five), malaria (three), acute gastroenteritis (two), phlebitis (one), pneumonia (one), and lymphocytic meningitis (one). Likewise, in an appraisal of the precipitating events in the recurrent cases of rheumatic fever, sore throat, injury, severe exposure, and occasionally malaria occurred in approximately the same proportion as the foregoing.

The physical findings in 102 patients (42 per cent) of the group with newly acquired rheumatic fever indicated cardiac involvement, usually of rather mild degree, as would be expected at this age; the majority were in the second decade of life. The remaining 140 patients showed no physical signs of cardiac involvement.

There remain 246 patients in the active rheumatic fever group whose illness represented a recurrence of previously known rheumatic infection. This ratio is in accord with the well-known tendency of the disease to recur, especially under the adverse circumstances of exposure and infection. From the point of view of the Army, our chief interest in scrutinizing this group has been to evaluate certain clues which might have been helpful in excluding them from foreign service. First, 106 of this group had chronic valvular heart disease antedating

their military service and known to the patients as a result of premilitary examinations. Certainly in the majority this should have been promptly suspected by history and recognized by physical examination either at the time of induction or during subsequent examinations in the service. Second, a review of the rheumatic fever history of this group is enlightening in that in addition to the overseas illness, thirty-five of these patients (of whom twenty-one also had rheumatic heart disease) had had rheumatic fever since entry into the service and had been treated for it in Army hospitals in the United States. Notwithstanding this, they were later dispatched overseas, the majority with combat units. In one extraordinary (and we believe exceptional) instance a soldier 20 years of age with known rheumatic heart disease since the age of 12 years was treated three weeks for severe acute rheumatic fever and well-marked chronic valvular heart disease of both the aortic and mitral valves at a station hospital while staging in one of the largest camps in the New York area. Presumably because of pressure from his unit, this soldier was discharged from the hospital in order to accompany his organization overseas. He spent the crossing in the ship's sick bay and on arrival in North Africa was sent directly to a general hospital where he continued to exhibit both clinical and laboratory evidence of rheumatic fever. He was returned promptly to the Zone of the Interior. We have encountered only one other similar instance of a soldier having been allowed to continue to his overseas destination after having been hospitalized for rheumatic fever at the staging area prior to embarkation. The foregoing represents the ultimate in mismanagement of these cases; nevertheless, lesser degrees of such have occurred sufficiently often to warrant emphasis at this time.

Further inquiry into the history of this group revealed that twelve additional patients (seven with known rheumatic heart disease) had had previous rheumatic fever within one year of entry into service, nine patients (five with rheumatic heart disease) had had previous rheumatic fever within two years of entry into service, and sixty others (forty-six with rheumatic heart disease) had given a history of two or more, and, in some instances, as many as six, previous attacks of rheumatic fever. It seems to us, at least in retrospect, that in the majority of these patients their susceptibility to rheumatic fever should have been recognized by history and by physical examination at some stage in their military career prior to their arrival overseas, even though it escaped detection at the time of induction. At least the thirty-five who were actually hospitalized for rheumatic fever in military installations in the United States should have been removed from units destined for foreign service.

The severity of rheumatic fever as it has occurred overseas has been of a mild to moderate degree in the majority of cases. Acute migratory polyarthritis responding to salicylate therapy has been the most frequent clinical feature. Relatively few have shown the manifestations often encountered with the more severe forms of rheumatic fever, especially as seen in childhood. Of these more serious manifestations, congestive heart failure occurred in four, pericarditis in eleven, pleuritis associated with pericarditis in four, pneumonitis associated

with other signs of severe rheumatic fever including a delayed auriculoventricular conduction time of 0.50 second in one, and high-grade heart block of 0.30 second or more in four patients, one of whom under observation later developed complete auriculoventricular dissociation. One patient 24 years of age exhibited typical rheumatic nodules over the bony prominence of the extremities, and one other patient, 23 years of age, had a fourth recurrence of typical Sydenham's chorea. In no instance was a death from rheumatic fever recorded, although it was a complicating feature in the patient whose clinical course was briefly noted in the discussion of post-mortem data in the preceding section.

Rheumatic Heart Disease.—Rheumatic heart disease manifested by the characteristic physical signs of valvular deformity was present in 600 patients (71 per cent) of the clinically analyzed series (Table V). In evaluating the thoroughness of the screening of Army personnel for the purpose of helpful criticism thereof, it is of interest that 273 (or 45 per cent) of this group had knowledge of their valvular disease before induction. In the majority (191 patients) this knowledge was acquired at the time of their childhood rheumatism or at subsequent school examinations; in others (thirteen patients), as a result of insurance or industrial examinations; and by some (twenty-five patients), because they had been rejected on this account by other branches of the Armed Forces before their ultimate induction. In eleven instances the presence of heart disease was recognized at the time of induction but, according to these patients, after considerable discussion and consultation they were accepted. In only two instances did patients state they were accepted without an examination.

Active rheumatic infection discussed in the preceding section was also present in 247 of this group and largely determined the management and disposition of these patients (Table V). There remained, however, 353 patients with chronic valvular disease of the rheumatic type without clinical or laboratory evidence of concurrent rheumatic fever. This group with so-called inactive rheumatic heart disease consisted of those who were hospitalized because of symptoms directly referable to the heart (in 228 instances) and those whose heart disease was recognized as an incidental finding during hospitalization for other unrelated disease or injury (in 125 instances).

The extent of involvement of the heart in 600 patients whose records were available for review is indicated in Table VI. Cardiac enlargement was present in 162 patients (27 per cent). In the majority it was of slight to moderate degree. Valvular disease in this group differed in no significant fashion from that observed in similar series for this age group in civilian practice. For example, in a series of 1,097 patients in New England (White and Jones) in whom valvular disease was sufficient or definite enough to be diagnosed clinically, 56.3 per cent were thought to have mitral valve disease alone as compared with 69 per cent for the present series, 14.7 per cent aortic alone as compared with 12 per cent, and 28.9 per cent both aortic and mitral as compared with 19 per cent here.⁴ The relative incidences of uncomplicated mitral stenosis and of slight aortic regurgitation are a trifle greater in this group than is ordinarily encountered, and in like fashion

TABLE VI. RHEUMATIC HEART DISEASE (EXTENT OF INVOLVEMENT IN 600 PATIENTS)

Combined lesions, mitral and aortic		112 (19%)
Mitral involvement		419 (69%)
(a) Regurgitation and stenosis	174	
(b) Regurgitation	145	
(c) Stenosis	100	
Aortic involvement		69 (12%)
(a) Regurgitation (Slight)	41	
(b) Regurgitation (Free)	12	
(c) Regurgitation and stenosis	16	

combined lesions of the aortic and mitral valves occurred less frequently than is commonly noted in similar studies. The explanation for these slight discrepancies we believe is evident. In the first instance it is well to remember that the diastolic murmur characteristic of mitral stenosis is notoriously difficult to recognize by the inexpert, especially if the patient is not examined recumbent and after exercise. Likewise, the soft blowing diastolic murmur best heard along the left sternal border indicative of slight aortic regurgitation is easily overlooked. It is to be expected then that the number of patients with these two isolated lesions which most easily escape detection in hurried examinations would appear relatively more frequently in the group under consideration. Contrariwise, combined valvular lesions are more easily detected and thus the majority should have been eliminated from this series. No instance of tricuspid or of pulmonary valve disease was recognized, and because of their relative rarity it is unlikely that such have occurred.

There remain the 241 patients in the active rheumatic fever group whose heart escaped demonstrable damage (Table V). These are classified as having potential rheumatic heart disease and require no special comment at this time. It is of passing interest, however, that 23 of this group had abnormally long auriculoventricular conduction times of 0.20 second or more by electrocardiogram during their rheumatic fever. In one instance the P-R interval measured 0.30 second. It is to be expected that approximately 25 per cent of this group in the course of months or years will show signs of valvular heart disease.⁵

Complications.—The more serious complications of rheumatic heart disease are auricular fibrillation, congestive failure, embolism, and subacute bacterial endocarditis. The period of overseas hospital observation of the patients in the present series is relatively short, averaging from one to two months, and the majority of the cases represent relatively mild degrees of heart disease as compared with the usual hospital series in civilian practice. Therefore the incidence of these important complications would naturally be low.

Auricular fibrillation was present in eight patients, all of whom had extensive rheumatic heart disease with well-marked mitral stenosis. In none was active

rheumatic fever a factor in precipitating the arrhythmia, and in three instances it was paroxysmal in nature. An additional patient with severe rheumatic heart disease had occasional episodes of paroxysmal auricular tachycardia.

Congestive heart failure occurred in only three patients. It was precipitated by a recurrent episode of rheumatic fever in two instances similar in this respect to the relationship commonly observed in childhood. The third patient was 44 years of age and had been in the Army for twenty-five years. He had well-marked cardiac enlargement with regurgitation and stenosis of both the mitral and aortic valves, undoubtedly of many years' standing. He denied knowledge of existing heart disease. The onset of auricular fibrillation precipitated congestive failure which responded satisfactorily to rest, digitalis, and diuretics. Acute pulmonary edema, the result of flooding of the lungs behind a tight mitral stenosis, so commonly observed in severe rheumatic heart disease in civilian practice, was not encountered in this series.

Embolus from the heart (dilated left auricle) to the peripheral circulation occurred in three patients, all of whom had high-grade mitral stenosis and auricular fibrillation. In the first instance, a soldier, 35 years of age, with known rheumatic heart disease since the age of 22, was brought to the hospital with hemiplegia. The second was a soldier 25 years of age with hemiplegia and aphasia. The third was a soldier 48 years of age with eight years' service, in whom the onset of auricular fibrillation was followed in a few days by an embolus to the popliteal artery. Pulmonary embolus, which may arise from a thrombus in dilated right heart chambers but most often comes from a thrombosed vein in the legs or pelvis from venous stasis secondary to heart trouble, was not encountered in this series.

Subacute bacterial endocarditis occurred in four patients with chronic rheumatic heart disease. In all instances the causative organism was the *Streptococcus viridans*. Two of these patients succumbed in this Theater before they could be evacuated to the Zone of the Interior. Post-mortem examination confirmed the clinical diagnosis in each. The remaining two patients whose illness had been present for approximately one month were transferred to the United States.

Angina pectoris was present in three patients 26, 29, and 44 years of age, respectively, each of whom had free aortic regurgitation. It is of interest that the eldest member of this group had been in the service for twenty-two years and had, in addition to aortic regurgitation, well-marked mitral stenosis and regurgitation.

Cardiac neurosis and neurocirculatory asthenia with predominant cardiac symptoms are notoriously common in combat troops. Knowledge of the presence of a cardiac murmur, no matter how innocuous the latter may be, often serves as the focus of a disabling neurosis. In the patients of this series with rheumatic heart disease, there were thirty-eight with disabling neuropsychiatric disorders. In seventeen of these, the symptoms were largely referred to organs of the body

other than the heart. In the remaining twenty-one, however, the complaints were those of neurocirculatory asthenia in eleven, and more clearly of cardiac neurosis in ten. In none of these was the nature or extent of the valvular disease sufficient to cause symptoms *per se*.

DISPOSITION

It was the established policy in this Theater that patients with rheumatic fever be returned to the United States. In the course of the present survey, certain deviations from this general rule have been noted in occasional instances, and the follow-up data indicate a sufficiently high incidence of recurrent attacks in those who, for one reason or another, were not evacuated to the Zone of the Interior to support amply the wisdom of the basic recommendation both for the welfare of the patient and the best interests of the Army. In regard to chronic valvular heart disease without active rheumatic fever, the policy was slightly more elastic in that those with minimal lesions and no cardiac symptoms were, in some instances, retained in the Theater, usually in a limited service capacity, and, under special circumstances, were even returned to full duty. In Table I we have included the disposition figures for the composite group of patients (those with rheumatic fever and rheumatic heart disease) from the general hospitals. It will be noted that 87.6 per cent were returned to the Zone of the Interior, 6.1 per cent were reclassified for limited service and retained in the Theater, and the remaining 6.3 per cent were returned to full duty. As is evident from Table I, the disposition policy of the various hospitals varied slightly from one extreme, illustrated by that of the 45th General Hospital, where all patients with either rheumatic fever or inactive rheumatic heart disease were automatically returned to the United States to another, illustrated by that of the 37th General Hospital, where only 67.6 per cent were returned to the Zone of the Interior. There was a grand total of 30,193 patients boarded for the Zone of the Interior from the medical service of the general hospitals listed in Table I. This figure includes all neuropsychiatric patients as well as a few with primarily surgical conditions. In spite of the distortion due to the factors noted in the foregoing, rheumatic fever and rheumatic heart disease accounted for 3.9 per cent of the total.

Disposition of the 353 patients with inactive rheumatic heart disease from the personally reviewed series was as follows: to the Zone of the Interior, 273 patients (77 per cent); to limited service, forty-nine patients (12 per cent); and to full duty, thirty-one patients (11 per cent). Those who were returned to full duty had very mild valvular lesions which were discovered incidentally during hospitalization for unrelated disease or injury, and in the majority of those assigned to limited service, the cardiac findings were minimal and not the limiting factor. There is no evidence, in so far as this study is concerned, that harmful effects have resulted in this small group of patients with minimal and inactive valvular disease as a result of their retention overseas. Nevertheless it was recognized that they were potential candidates for recurrent rheumatic fever and, to a lesser extent, for bacterial endocarditis.

CONCLUDING REMARKS

The "*line of duty*" status for this group of patients is of importance, for a considerable number may be expected with the passage of years to become cardiac invalids. In this connection there has been considerable variation in the criteria adopted by the different hospitals. In general, however, for those patients who developed rheumatic fever after entry into the service, irrespective of whether or not they had had previous attacks, the illness was considered "in line of duty." The group of patients with inactive rheumatic heart disease presented a more difficult problem and the policy of the different hospitals varied considerably on this score. In the absence of active rheumatic fever and if the history revealed an attack prior to entry into the service, or if the patient had knowledge of the existence of previous valvular disease, or if the physical signs indicated an advanced lesion which, from clinical experience, is known to require a minimum of several years to develop (for example, high-grade mitral stenosis) and the patient's Army service was of only one to two years, under any of these circumstances most of the general hospitals considered the valvular disease to have existed prior to entry into the service, even though it was not noted at the time of induction and hence was considered not "in line of duty." Whether or not this decision will be upheld when the question arises in the future will undoubtedly depend on the policy adopted at that time by the Veterans' Administration. The most difficult situation for a fair appraisal involved those patients with a relatively short Army career who developed acute rheumatic fever in the service but whose valvular disease by clinical judgment must have existed for many years. In these instances the policy followed by most of the hospitals was to consider the "line of duty" of the rheumatic fever as "yes" and of the advanced valvular disease as "no."

In reviewing the data recorded herein and from the personal experience in this Theater of those especially interested in the problem, as well as from the available data published from other Theaters,⁶ it is evident that the recommendations and the measures in force to exclude from overseas service individuals with chronic valvular disease and those especially susceptible to rheumatic fever have been highly effective. This conclusion is amply supported by a comparison with the experience from World War I. That mistakes have occurred is inevitable in view of the urgency which total war precipitated upon the nation. Our sole purpose in stressing the more obvious errors which in retrospect have come to our attention is of a constructive nature and can in no way detract from the superb effort and success of all concerned in excluding the majority of these patients from the Armed Forces.

Finally, and again in retrospect, if all of those with known heart disease and those who had had rheumatic fever within one year of entry into the service had been excluded, the problem presented to the Army in this Theater would have been reduced by 37 per cent. If, in addition, those patients who had a history of two or more attacks of rheumatic fever had also been excluded, this figure would be increased to 43 per cent. This represents perhaps an ideal but impractical solution in the face of a war for survival.

SUMMARY AND CONCLUSIONS

A survey has been made of the incidence, clinical features, and disposition of rheumatic fever and rheumatic heart disease in Army personnel in the North African and Mediterranean Theater of Operations from the original landings in November, 1942, through the Tunisian, Sicilian, and Italian campaigns to the end of hostilities in May, 1945.

1. Reliable statistical data drawn largely from the experience of the seventeen general hospitals in this Theater indicate that approximately 1,400 patients have been hospitalized, of whom more than one-half had active rheumatic fever and the remainder, inactive rheumatic heart disease.

2. A review of the protocols of 1,507 consecutive post-mortem examinations disclosed thirteen instances of healed rheumatic valvular disease of minimal extent and two instances of active rheumatic carditis, an incidence of .9.9 per 1,000.

3. The clinical features of rheumatic fever and valvular heart disease in a series of 841 patients whose records were personally reviewed reveals that 58 per cent had active rheumatic infection and the remaining 42 per cent, inactive valvular disease. The latter was discovered in the majority as an incidental finding during hospitalization for unrelated disease or injury. The initial onset of rheumatic fever appeared to have originated in this Theater in 242 (50 per cent) of those with active disease.

4. In those in whom valvular disease was found, this complication was, in general, of a mild to moderate degree, and its existence prior to military service was known to 45 per cent of the group. Of the more serious complications, auricular fibrillation was present in eight patients, congestive heart failure in three, embolism in three, and subacute bacterial endocarditis in four.

5. The established policy in this Theater was that all patients with rheumatic fever be evacuated to the Zone of the Interior. In regard to inactive rheumatic heart disease of minimal degree, the policy was more elastic. In the present survey it was found that 92.8 per cent of those with rheumatic fever had been returned to the United States, 3.7 per cent reclassified for limited service, and 3.5 per cent returned to full duty. Comparable figures for those with inactive rheumatic heart disease were 77 per cent, 12 per cent, and 11 per cent, respectively.

6. Rheumatic fever and rheumatic heart disease accounted for 3.9 per cent of 30,193 patients boarded for the Zone of the Interior from the medical service of the general hospitals in the Theater.

7. As a result of this survey, which is supported by published data from other Theaters, it is evident that the measures now in force to exclude from foreign service individuals with chronic valvular disease and those especially susceptible to rheumatic fever have been highly effective.

8. In retrospect, if those patients with known heart disease and those who had had rheumatic fever within one year of entry into the service had been

excluded, the problem presented to the Army in this Theater would have been reduced by 37 per cent.

The interest and advice of Colonel Perrin H. Long, Medical Consultant to the Surgeon, Mediterranean Theater of Operations, United States Army, made possible this study. The chiefs of the medical service of the general hospitals in the Theater rendered invaluable aid by consultation and by letter.

REFERENCES

1. Clawson, B. J.: Incidence of Types of Heart Disease Among 30,265 Autopsies, With Special Reference to Age and Sex, *AM. HEART J.* **22**: 607, 1941.
2. Scott, R. W., and Garvin, C. F.: Incidence of Types of Heart Disease Among 6,548 Autopsies, With Observations on Race and Sex. Presented before the American Heart Association, Cleveland, 1941.
3. The Medical Department of the United States Army in the World War, Vol. XV, War Department, Washington, D. C., 1925, Senate Library.
4. White, P. D., and Jones, T. D.: Heart Disease and Disorders in New England, *AM. HEART J.* **3**: 302, 1928.
5. Bland, E. F., and Jones, T. D.: The Delayed Appearance of Heart Disease After Rheumatic Fever, *J. A. M. A.* **113**: 1380, 1939.
6. (a) Sprague, Howard B., and McGinn, Sylvester: Heart Disease and Disorders as Causes for Evacuation From the South Pacific Combat Area, *AM. HEART J.* **4**: 563, 1944.
(b) Delaney, Joseph H., Miller, Samuel J., Kimbro, R. W., and Bishop, L. F., Jr.: Valvular Heart Disease Previously Unrecognized in Military Medical Examinations, *J. A. M. A.* **123**: 884, 1943.

NOTES ON THE SIMILARITY OF QRS COMPLEX CONFIGURATIONS IN THE WOLFF-PARKINSON-WHITE SYNDROME

GEORGE E. BURCH, M.D., AND J. LEROY KIMBALL, M.D.
NEW ORLEANS, LA.

IN THE Wolff-Parkinson-White syndrome the QRS complexes vary in the standard leads and have a tendency to repeat their configurations with considerable frequency. It is the purpose of this paper merely to indicate these various patterns and to give some possible explanations. The significance of these variations is not completely understood. It is intended to call to the attention of others this tendency of the patterns of the QRS complexes in the Wolff-Parkinson-White syndrome to fall into fairly definite groups so that additional data concerning them may be accumulated with the idea of better understanding the nature and significance of the syndrome. Furthermore, the QRS configurations often resemble electrocardiograms seen in conditions which are of a serious nature and which may be confused with the less serious Wolff-Parkinson-White syndrome. Complete left bundle branch block is one serious condition that has been erroneously diagnosed when the true state was the Wolff-Parkinson-White syndrome (Fig. 3). It is important that such errors be avoided.

The electrocardiograms available for study in this laboratory and in the literature reviewed¹⁻³² contained few precordial leads. For that reason the present report is limited to the standard leads.

All of the electrocardiograms presented the criteria for the diagnosis of the Wolff-Parkinson-White syndrome. In summary these were (1) shortening of the P-R interval (the P-R segment in particular) and a prolongation of the QRS duration with slurring and notching; (2) absence of any clinical signs of heart disease in most instances; (3) occurrence of repeated paroxysms of tachycardia; and (4) return of the electrocardiogram to normal on parasympathetic depression and exercise, as well as spontaneously.

For the purpose of this discussion, the features of the configurations of the QRS complexes of the electrocardiograms evident during the period of aberrant conduction are divided into five types. They are as follows:

Type I.—The QRS complex on first glance appears to be fairly normal. In Lead I the QRS abnormality is limited to the initial portion. It is slurred and otherwise slightly deformed near the isoelectric line. The QRS complexes in this lead consist almost entirely of an R wave of great magnitude. The QRS complex in Lead II shows initial slurring near the base line, while that in Lead III

From the Department of Medicine, Tulane University School of Medicine, and Charity Hospital, New Orleans, La.
Received for publication Dec. 17, 1945.

is abnormally wide but not necessarily slurred or deformed. There may be slight left-axis deviation (Fig. 1).

Type II.—There is marked left-axis deviation of the QRS complex. The QRS complex in Lead I consists mainly of an R wave of great magnitude, while

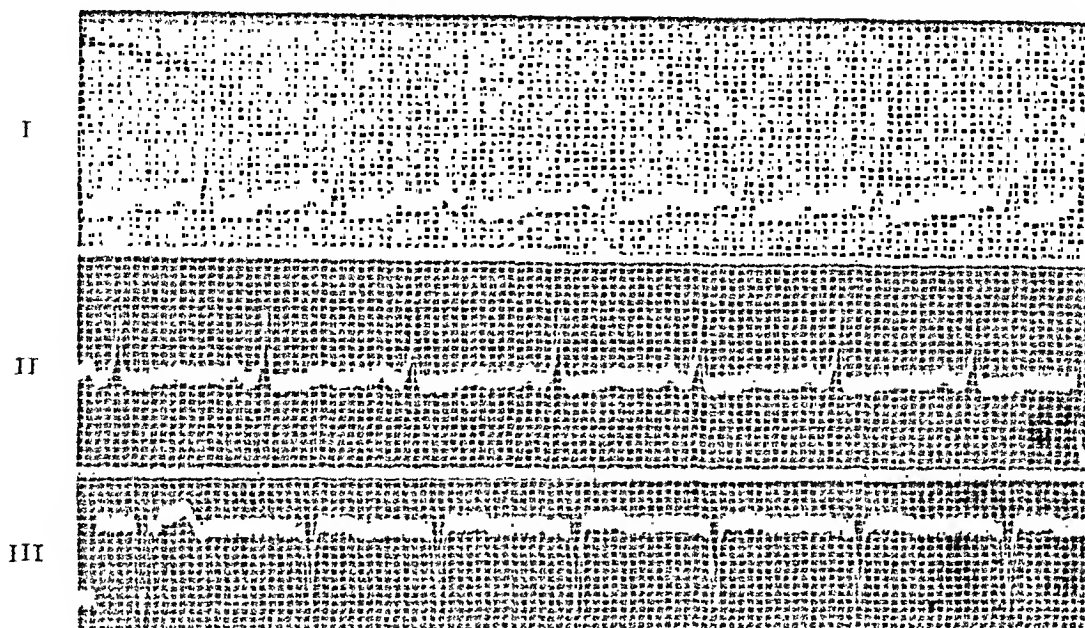


Fig. 1.—Type I pattern with slight deformation limited to the initial portion of the QRS complex.

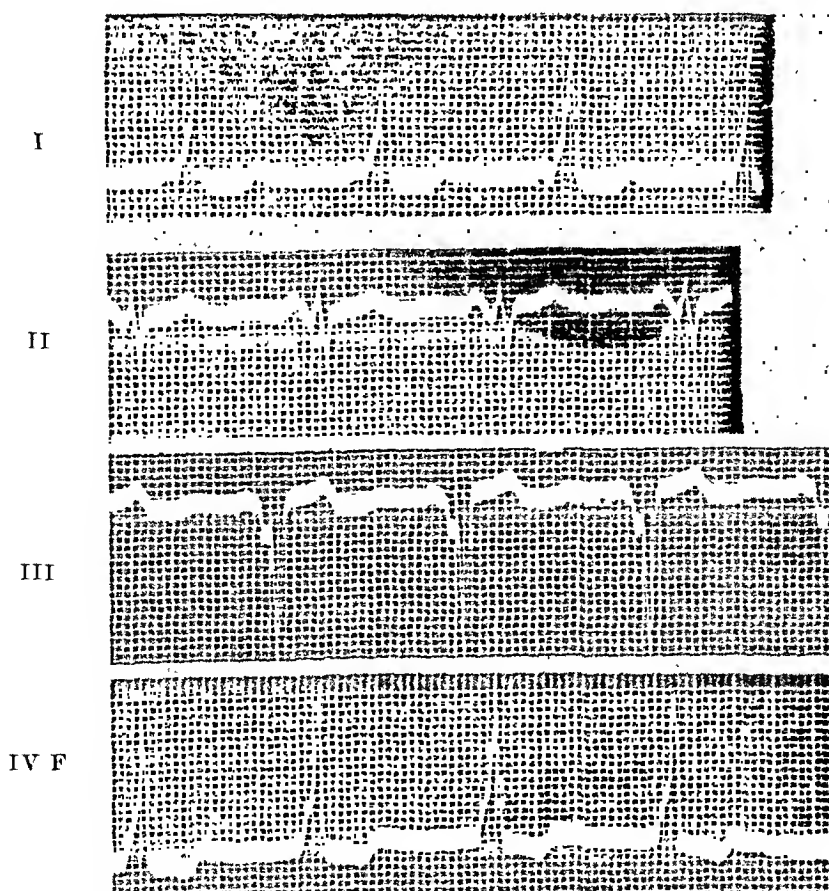


Fig. 2.—Type II pattern with marked left axis deviation of the QRS complex.

in Lead III, an S wave of great magnitude is the conspicuous feature. The QRS in Lead II consists of an R and S wave of relatively low but equal amplitude. There is slurring and various deformations of the QRS complex in Leads I, II, and III. Those abnormalities may not be as obvious in Lead II as in the other leads. A typical tracing is shown in Fig. 2.

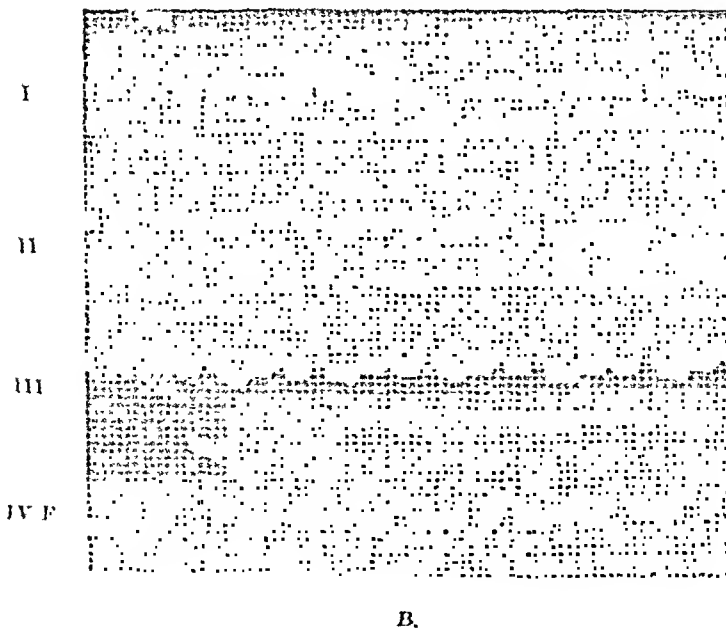
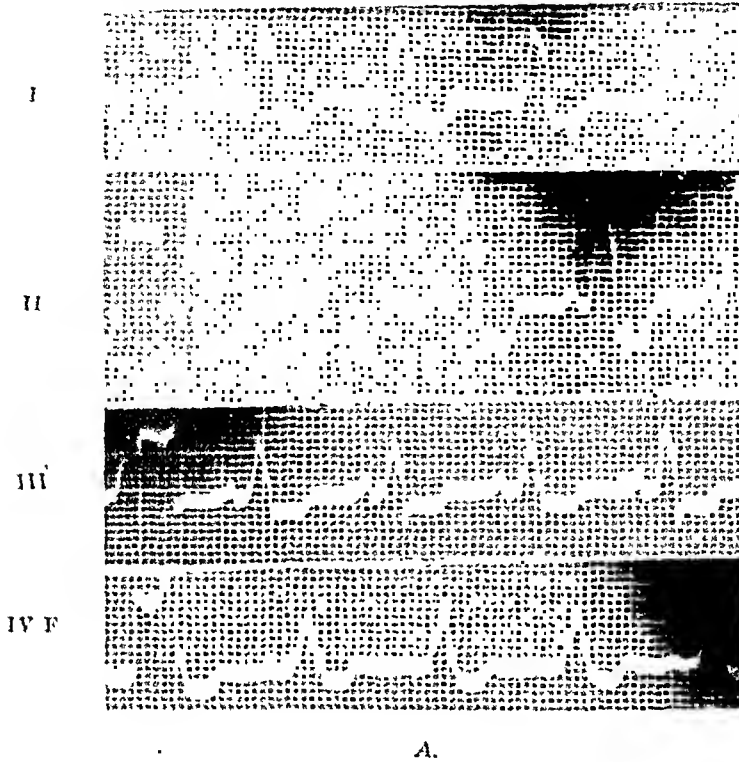


Fig. 3.—Type III pattern resembling left bundle branch block.

Type III.—The pattern of the QRS complex in all standard leads, and, of course, particularly in Lead I, resembles very closely complete left bundle branch block. The resemblance to left bundle branch block is so marked that it is very easy to overlook the syndrome. The short P-R interval suggests the correct entity. The QRS complex is slurred and variously deformed throughout its duration; the slurring and notching is not limited to the first part of the complex. As in true complete left bundle branch block, the main deflection (the one of greatest duration) of the QRS complex in Lead I is upright (Fig. 3).

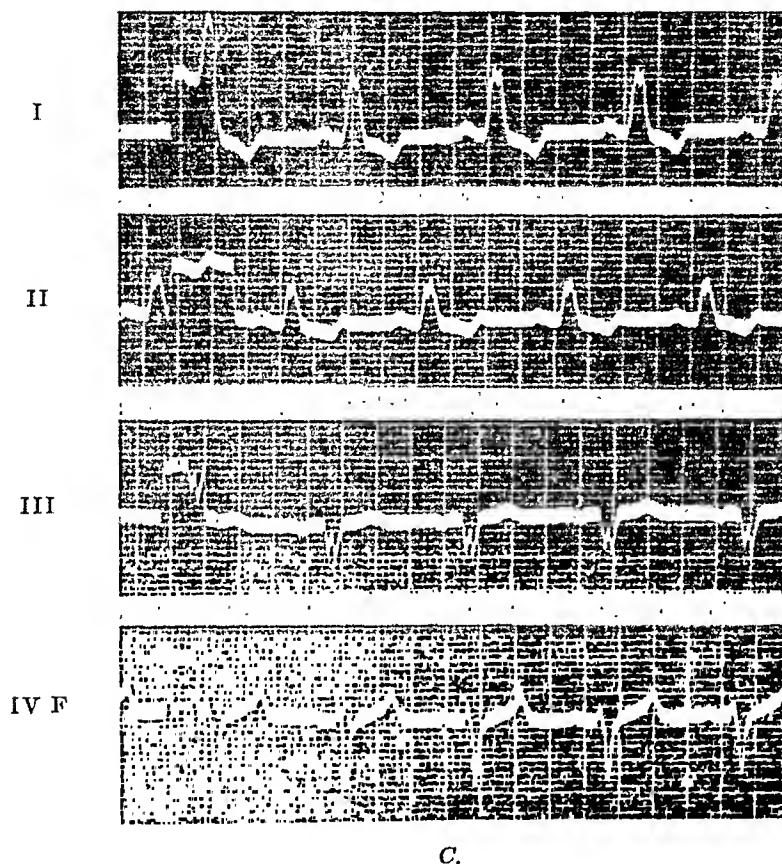


Fig. 3 (Cont'd).—For complete legend, see opposite page.

Type IV.—In this type the QRS pattern in Lead I resembles true complete right bundle branch block. The terminal portion of the QRS complex is an S wave of great duration. It is this portion of the QRS complex that is especially slurred and deformed. A slurred R wave of low amplitude in Lead I is usually present. The QRS complexes in Leads II and III are deformed terminally as well as initially. There have been only a few such types reported in the literature, none having been encountered by the authors personally. Fig. 4 is a typical illustration of this QRS pattern. A case reported by Vakil³⁰ appears to be a true right bundle branch block rather than a Wolff-Parkinson-White syndrome.

Type V.—This group consists of QRS patterns of *normal duration* in all three standard leads. The short P-R interval in all leads suggests the correct syndrome. If patients with such electrocardiograms are followed, subsequent

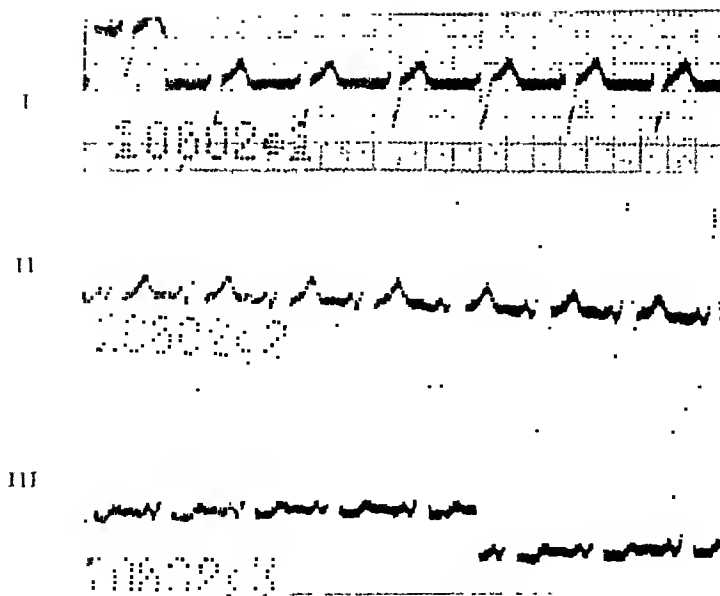


Fig. 4.—Type IV pattern resembling right bundle branch block.

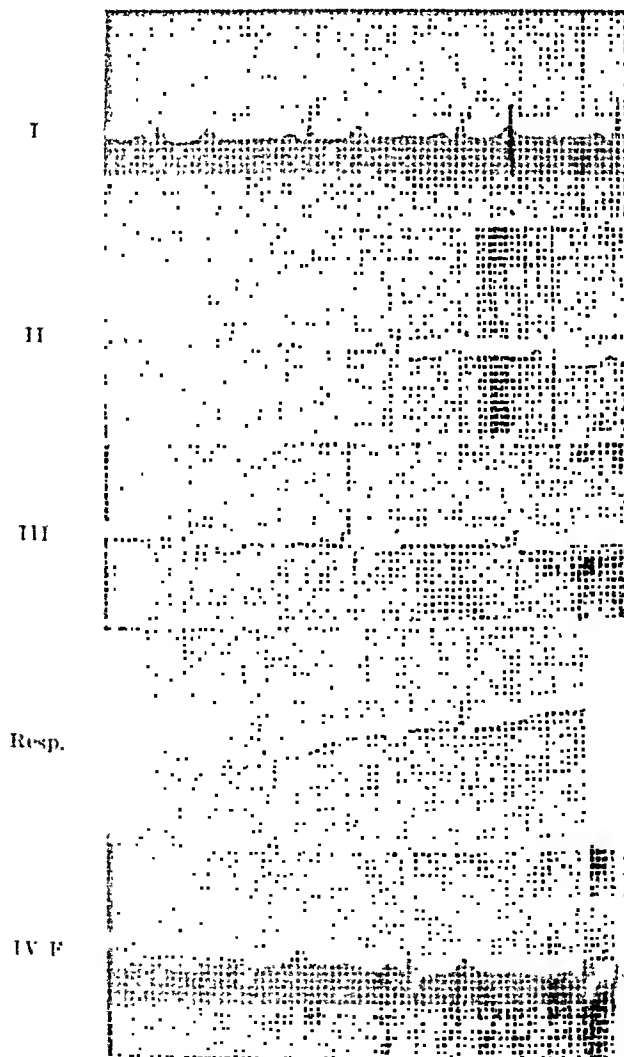


Fig. 5.—Type V pattern with the QRS complexes of normal duration in all leads suggesting essentially normal order of ventricular depolarization.

tracings may show the P-R interval to revert to normal and the QRS complex to alter its configuration simultaneously. The cases reported by Fox³¹ and by Öhnell³⁴ are the only examples of such an electrocardiogram encountered in the literature. In our personal experience one (questionable) similar electrocardiogram was noted (Fig. 5). The second cardiac cycle of Lead III during deep inspiration (Fig. 5) was initiated by an auricular ectopic focus. This resulted in a normal P-R interval and a change in the order of ventricular depolarization indicated by the change in the QRS complex to a more normal appearance. This is in support of the Wolff-Parkinson-White syndrome. Although the QRS complex in this fifth type is of normal duration, it may or may not be recognizably deformed. When there are only slight changes in the order of ventricular depolarization and the resulting deformity is minimal, this slight deformity is easily recognized when the mechanism reverts to normal and the normal QRS complex becomes apparent.

DISCUSSION

It is generally agreed that the Wolff-Parkinson-White syndrome is produced by an anomalous connection (cardiac muscle or neuromuscular pathway) between the atria and the ventricles.^{6,9,11} This results in an early activation of ventricular depolarization. The order of depolarization begins, at least, in an abnormal fashion. The site of initiation is determined by the site of connection of the anomalous pathway to the ventricle. As far as the initiation of ventricular depolarization is concerned, the net result is similar to the initiation of ventricular depolarization by an impulse originating in an ectopic focus in the ventricular musculature as in ventricular ectopic beats. In the case of ventricular premature contractions, ventricular depolarization is not completed by an impulse entering the Purkinje system later from the atrioventricular node as is the case in the Wolff-Parkinson-White syndrome. It is well to remember that combination complexes (QRS) may even resemble those of the Wolff-Parkinson-White syndrome if an ectopic focus in the ventricles initiates ventricular depolarization late in the cardiac cycle and the normal impulse from the auricle enters the ventricle from above via the normal pathways to complete ventricular depolarization. The number of sites of origin of ventricular depolarization in ventricular premature contractions is unlimited, and the resultant variations in configurations in the recorded QRS complexes are likewise unlimited. This is essentially true also for the Wolff-Parkinson-White syndrome. However, in this syndrome, because of the nature of the anomalous pathway, the ventricular terminus (anatomic and electrical) is near the base of the ventricle (it is quite unlikely, though conceivably possible, for the anatomic and electric terminus to be near the apex of the heart). For that reason the initial process of ventricular depolarization in the Wolff-Parkinson-White syndrome should resemble in all respects the initial process of a ventricular premature beat initiated by an ectopic focus located in the base of the ventricle which is the site of termination of the anomalous pathways. The records in the completed electrocardiograms should resemble each other.

The order of depolarization and the configuration of the QRS in the completed electrocardiogram is also influenced by the relation of the site of termination of the anomalous pathway to the epicardial and endocardial surfaces.

From the foregoing discussion, it is obvious that the QRS patterns in the Wolff-Parkinson-White syndrome should bear a relation to the QRS patterns in ventricular premature contractions. If the anomalous pathway ends in the right ventricle, the initial slurred portion of the QRS complex is upright in Lead I. In the studies of Rosenbaum and associates⁹ the slurred abnormal portion of the QRS complex in Lead I was found to be upright and the anomalous pathway was found to terminate in the base of the heart more in the right half of the muscle mass. Wood and Wolferth²⁰ were fortunate enough to study histologically the heart of a patient who in life had an electrocardiogram presenting the Wolff-Parkinson-White syndrome. The slurred and deformed portion of the QRS in Lead I was upright and the serial sections of the heart showed the anomalous pathway to terminate in the base of the right ventricle. Öhnel¹⁸⁴ also found an anomalous band of muscle connecting the left atrium to the left ventricle near the interventricular septum. The electrocardiogram, as would be expected, resembled that of Type V discussed.

The fact that the QRS configurations in the Wolff-Parkinson-White syndrome fall into five types may be fortuitous in view of the fact that there are not many such cases available for analysis. It is quite possible, however, for the site of termination of the pathways to be fairly constant. Not until many electrocardiograms and much autopsy material have been accumulated will this be understood.

The configurations of the QRS depend upon the order of ventricular depolarization. In the Wolff-Parkinson-White syndrome the QRS complex is essentially a combination complex, as mentioned previously. There is a force of depolarization produced by a depolarization process initiated in the ventricles at the terminus of the anomalous pathway and another force of depolarization produced by a depolarization process in the ventricles initiated in a normal fashion in the remaining polarized resting muscle by an impulse reaching the ventricle via the A-V node and Purkinje system. It is obvious that the relative times of initiation and duration of these two processes of depolarization will influence the qualities of the forces involved and the configuration of the QRS complexes in the completed electrocardiogram. For example, if an anomalous pathway terminates in the base of the right ventricle, an impulse entering this pathway will initiate depolarization of the right ventricle. Because of the position of this ventricle in relation to the right-arm and left-arm electrodes of Lead I, an abnormally shaped QRS complex with relatively small manifest magnitude is inscribed in the completed electrocardiogram. Should the A-V node delay the normally progressing impulse from the S-A node for 0.15 or 0.16 second, sufficient time will have elapsed for practically all of the free wall of the right ventricle and most of the septum completely to be depolarized by the aberrant impulse. Now, when the normal impulse enters the ventricle, the depolarization process

is not only completed in a more or less normal fashion, but a marked left-axis (mean) deviation of the QRS complex results. This marked left-axis deviation is to be expected since the electromotive force created by the depolarization process in the left ventricle exists almost alone or alone; that is, free from any neutralizing influences by forces of depolarization in the right ventricle which has already been depolarized from the anomalous pathway. Because of the mass of muscle in the left ventricle and the position of the wall of this ventricle in relation to the right-arm and left-arm electrodes of Lead I, the manifest magnitude of the QRS axis is great terminally. This reasoning offers an explanation for the Type II QRS complexes (Fig. 2). A study of the cases reported in the literature in which electrocardiograms were taken with and without conduction through the anomalous pathways support the foregoing explanation.^{9, 11-21}

In the Type I (Fig. 1) QRS pattern, the delay of the impulse from the auricles by the A-V node must be relatively short (about 0.15 second in most instances) so that the process of ventricular depolarization initiated via the anomalous pathway is of relatively short duration; under these circumstances most of ventricular depolarization is initiated via the impulse from the A-V node. From a study of the cases with and without function of the anomalous pathway reported in the literature, this appears to be true.¹⁻⁸

This same argument can explain the QRS configurations of Types III and IV (Figs. 3 and 4). In order for the slurring and various types of deformities in the QRS complexes to occur throughout or almost throughout the duration of the QRS complex, the depolarization process initiated at the terminus of the anomalous pathway must progress through all or most of the ventricles uninfluenced by another depolarization process initiated by an impulse traveling in a normal fashion via the A-V node. This would occur if the A-V node conduction at the time were relatively slow, 0.18 second or longer. The influences of digitalis³³ in delaying A-V conduction and increasing the duration of the depolarization process initiated via the anomalous pathway is in support of the foregoing argument. If this be true, the QRS complexes should closely resemble ventricular premature contractions. Impulses entering the right ventricle via an anomalous pathway should resemble right ventricular premature contractions. In fact, the QRS complexes with the main deflections positive in all three standard leads in Fig. 3 and with the secondary type of T wave changes have the characteristics of right ventricular premature contractions initiated by a focus in the base of the right ventricle. Similarly, the QRS complexes in Fig. 4 resemble left ventricular premature contractions.

In support of the idea of relatively delayed A-V conduction explaining tracings of Types III and IV, Figure 3, A is shown. In this figure the P-R interval during the normal mechanism is from 0.18 to 0.20 second. When this time interval is measured after the beginning of the P waves in Fig. 3, it is noted that an impulse could not have entered the ventricles until they were almost completely depolarized by means of the then functioning anomalous pathway. In fact, by 0.18 to 0.20 second from the beginning of the P waves of Fig. 3 the

ventricular musculature is so completely depolarized that the muscle could not even respond to a stimulus that might present itself via the A-V node. A study of tracings of Types III and IV reported in the literature for periods of functioning and nonfunctioning anomalous pathways showed P-R intervals or A-V delays which support the foregoing argument.²²⁻³⁰

The importance of timing of the two depolarization processes in Wolff-Parkinson-White syndrome is evident. The marked tendency for A-V node conduction (P-R interval) to vary in health and disease and under the influence of drugs is well known. In view of the marked variations in the delay of auricular impulses in the A-V node, it is not surprising that upon this basis alone the QRS complexes in Wolff-Parkinson-White syndrome should be so variable and a QRS tracing of Type I should change to one of Type III. If the matter of timing were the only important factor concerned with the production of variations in the QRS configurations, it would be possible to classify the configurations of the recorded QRS complexes on relative timings of impulse conduction via the anomalous and A-V node pathways. There are, however, several other factors of importance which can influence the configuration of the QRS complexes. The integration of such factors as anatomic rotation of the heart, multiple pathways functioning simultaneously or separately which terminate in various portions of the ventricle, along with variations in delay in A-V conduction, certainly must contribute to the variations in the QRS pattern from patient to patient or from moment to moment within the same patient.

From the configuration of the QRS complexes in the standard leads, it is possible to have only a general impression of the site of termination of the pathways. In Type V (Fig. 5) the QRS complexes are of normal duration and may or may not be recognizably deformed. The rather normal or normal-appearing QRS complex during the abnormal mechanism indicates a fairly normal order of ventricular depolarization. For the order of ventricular depolarization to be about normal, the abnormal pathway must have terminated in the inter-ventricular septum near its base, in the bundle of His, or in either of the main branches near the bundle of His. Such an anatomic termination of the anomalous pathway is quite possible and is a probable explanation for the Type V tracing (Fig. 5). The finding in Öhnell's patient of a QRS complex of normal duration and only slight deformation and on serial section a short (6 mm. in length) anomalous bundle terminating near the base of the left ventricle near the septum is certainly in support of the hypothesis presented to explain the Type V tracings.

Finally, the tendency for QRS patterns to repeat themselves is pointed out not for the purpose of recommending that the tracings be so classified for clinical purposes, but merely to indicate this tendency in order to lead to a better discussion and presentation of some of the physiologic concepts of the Wolff-Parkinson-White syndrome. Öhnell³¹ has made an extensive and detailed study of the various electrocardiographic patterns and has classified them on their configurations rather than on the electric events responsible for them. Obviously, if one considers minute details of configurations of the electrocardiograms,

the patterns can show unlimited variations. The five general types discussed reduce the configurations to more practical levels. Minute detailed descriptions based upon empirical rules seem to add little at this time.

SUMMARY

1. The tendency of the QRS configurations in Wolff-Parkinson-White syndrome to fall into five types is pointed out.

2. An analogy between the initiation of ventricular depolarization by the terminus of the anomalous pathway and a similarly located focus of a ventricular premature contraction is drawn.

3. An electrocardiogram of a questionable case of Wolff-Parkinson-White syndrome with normal-appearing QRS complexes is presented in Fig. 5. It is suggested that these QRS complexes were initiated by impulses reaching the ventricles via an anomalous pathway terminating in the center of the septum near its base or in the bundle of His.

4. Theoretic explanations are offered for the QRS patterns observed in the Wolff-Parkinson-White syndrome.

REFERENCES

Type I

1. Rosenbaum, F. F., Hecht, H. H., Wilson, F. N., and Johnston, F. D.: The Potential Variations of the Thorax and the Esophagus in Anomalous Atrioventricular Excitation (Wolff-Parkinson-White Syndrome), *AM. HEART J.* 29: 281, 1945. (Cases 1 and 4.)
2. Wolff, L., Parkinson, John, White, P. D.: Bundle-Branch Block With Short P-R Interval in Healthy Young People Prone to Paroxysmal Tachycardia, *AM. HEART J.* 5: 685, 1930. (Cases 2, 3, 4, 6, 7.)
3. Tung, C.: Functional Bundle-Branch Block, *AM. HEART J.* 11: 89, 1936. (Case 2.)
4. Wedd, A. M.: Paroxysmal Tachycardia, *Arch. Int. Med.* 27: 571, 1921. (Case 1.)
5. Pearson, J. R., and Wallace, A. W.: The Syndrome of Paroxysmal Tachycardia With Short P-R Interval and Prolonged QRS Complex With Report of Two Cases, *Ann. Int. Med.* 21: 830, 1944. (Case 2.)
6. Wolferth, C. C., and Wood, F. C.: The Mechanism of Production of Short P-R Intervals and Prolonged QRS Complexes in Patients With Presumably Undamaged Hearts: Hypothesis of an Accessory Pathway of Auriculo-ventricular Conduction (Bundle of Kent), *AM. HEART J.* 8: 297, 1933. (Cases 4 and 9.)
7. Bishop, L. F.: Bundle Branch Block With Short P-R Interval in Individuals Without Organic Heart Disease, *Am. J. M. Sc.* 194: 794, 1937. (Case 1.)
8. Kaplan, G., and Cohn, T. D.: Syndrome of Auriculoventricular Accessory Pathway, *Ann. Int. Med.* 21: 824, 1944. (Case 2, R. W.)

Type II

9. Rosenbaum, F. F., Hecht, H. H., Wilson, F. N., and Johnston, F. D.: The Potential Variations of the Thorax and the Esophagus in Anomalous Atrioventricular Excitation (Wolff-Parkinson-White Syndrome), *AM. HEART J.* 29: 281, 1945. (Case 10.)
10. Wilson, F. N.: A Case in Which the Vagus Influenced the Form of the Ventricular Complex of the Electrocardiogram, *Arch. Int. Med.* 16: 1008, 1915. (Case C.)
11. Butterworth, J. S., and Poindexter, C. A.: Short P-R Interval Associated With a Prolonged QRS Complex, *Arch. Int. Med.* 69: 437, 1942. (Case T. B.)
12. Wolferth, C. C., and Wood, F. C.: Further Observations on the Mechanism of the Production of a Short P-R Interval in Association With Prolongation of the QRS Complex, *AM. HEART J.* 22: 450, 1941. (Case R. M. and Case A. B.)

13. Wolff, L., Parkinson, J., and White, P. D.: Bundle-Branch Block With Short P-R Interval in Healthy Young People Prone to Paroxysmal Tachycardia, *AM. HEART J.* 5: 685, 1930. (Cases 1, 3, 8, 10.)
14. Kaplan, G., and Cohn, T. D.: Syndrome of Auriculoventricular Accessory Pathway, *Ann. Int. Med.* 21: 824, 1944. (Case J. P.)
15. Sigler, L. H.: Functional Bundle-Branch Block (Partial) Paradoxically Relieved by Vagal Stimulation, *Am. J. M. Sc.* 185: 211, 1933. (Case 1.)
16. Movitt, E. R.: Some Observations on the Syndrome of Short P-R Interval With Long QRS, *AM. HEART J.* 29: 78, 1945. (Case W. A.)
17. Master, A. M., Joffe, H. L., and Dack, S.: Atypical Bundle Branch Block With Short P-R Interval in Graves' Disease, *J. Mt. Sinai Hosp.* 4: 100, 1937. (Case D. O.)
18. Hamburger, W. W.: Bundle Branch Block. Four Cases of Intraventricular Block Showing Some Interesting and Unusual Clinical Features, *M. Clin. North America* 13: 343, 1929. (Case 4.)
19. Spangenberg, J. J., Vedoya, R., and Gonzalez Videla, J.: Un Caso de QRS ancho y mellado con PR acortado, *Rev. argent. de cardiol.* 4: 244, 1937. (Case 1.)
20. Wood, F. C., and Wolferth, C. C.: Histologic Demonstration of Accessory Muscular Connections Between Auricle and Ventricle Short P-R Interval and Prolonged QRS Complex, *AM. HEART J.* 25: 454, 1943. (Case A. F.)
21. Wolferth, C. C., and Wood, F. C.: The Mechanism of Production of Short P-R Intervals and Prolonged QRS Complexes on Patients With Presumably Undamaged Hearts: Hypothesis of an Accessory Pathway of Auriculoventricular Conduction (Bundle of Kent), *AM. HEART J.* 8: 297, 1933. (Case 1, Fig. 2—Case 7.)

Type III

22. Rosenbaum, F. F., Hecht, H. H., Wilson, F. N., and Johnston, F. D.: The Potential Variations of the Thorax and the Esophagus in Anomalous Atrioventricular Excitation (Wolff-Parkinson-White Syndrome), *AM. HEART J.* 29: 281, 1945. (Case 8, Case 9.)
23. Sigler, L. H.: Functional Bundle Branch Block (Partial) Paradoxically Relieved by Vagal Stimulation, *Am. J. M. Sc.* 185: 211, 1933. (Case C. E.)
24. Wolff, L., Parkinson, J., and White, P. D.: The Bundle-Branch Block With Short P-R Interval in Healthy Young People Prone to Paroxysmal Tachycardia, *AM. HEART J.* 5: 685, 1930. (Case 5.)
25. Hunter, A., Papp, C., and Parkinson, J.: The Syndrome of Short P-R Intervals, Apparent Bundle Branch Block and Associated Paroxysmal Tachycardia, *Brit. Heart J.* 2: 107, 1940. (Case 1.)
26. Lynch, J. P., and McAllister, R. G.: The Wolff-Parkinson-White Syndrome, *Virginia M. Monthly* 70: 415, 1943. (Case R. S.)
27. Roberts, C. H., and Abramson, D. D.: Ventricular Complexes of the Bundle Branch Block-type Associated With Short P-R Intervals, *Ann. Int. Med.* 9: 983, 1936. (Case A. N.)
28. Pearson, J. R., and Wallace, A. W.: The Syndrome of Paroxysmal Tachycardia With Short P-R Interval and Prolonged QRS Complex With Report of Two Cases, *Ann. Int. Med.* 21: 830, 1944. (Case 1.)

Type IV

29. Tung, C.: Functional Bundle-Branch Block, *AM. HEART J.* 11: 89, 1936. (Case 1.)
30. Vakil, R. J.: A Case of Mitral Stenosis With Apparent Bundle Branch Block, Short P-R Intervals and Attacks of Paroxysmal Tachycardia, *Indian M. Gaz.* 77: 521, 1942.

Type V

31. Fox, T.: Aberrant Atrio-ventricular Conduction in a Case Showing a Short P-R Interval and an Abnormal But Not Prolonged QRS Complex, *Am. J. M. Sc.* 209: 199, 1945. (Case 1.)
32. Authors' case (Fig. 5).
33. Fox, T., Travel, J., and Molofsky, L.: Action of Digitalis on Conduction in the Syndrome of Short P-R Interval and Prolonged QRS Complex, *Arch. Int. Med.* 71: 206, 1943.
34. Öhnell, R. F.: Pre-excitation, A Cardiac Abnormality, Stockholm, 1944, *Acta Medica Scandinavica*, Supplement No. 152.

THE SYNDROME OF ABDOMINAL AORTIC ANEURYSM RUPTURING INTO THE GASTROINTESTINAL TRACT

SUMMARY OF THE LITERATURE AND CASE REPORT

HOMER H. HUNT, M.D., AND CARL V. WELLER, M.D.
ANN ARBOR, MICH.

RUPTURE of an aneurysm of the abdominal portion of the aorta into the gastrointestinal tract is accompanied by a characteristic syndrome which will usually suggest the diagnosis. This dramatic accident is sufficiently rare to justify the continued reporting and collection of cases for analysis. In this paper, another example of the rupture of such an aneurysm into the duodenum is recorded, and the list of reported cases is brought up to date.

Including the one reported here, forty-one cases have now been collected. Undoubtedly others are concealed in the numerous studies of aortic aneurysm in general. In 1943, Rottino,¹ in a very thorough search, found thirty-one examples of rupture of an abdominal aortic aneurysm and added a case of his own. The essential clinical and morphologic data concerning the group, so far as they were obtainable, were arranged by him in tabular form. Our Table I, adding nine cases, is purposely constructed as a continuation of that presented by Rottino, using the same headings and continuing his serial numbering. Since the cases reported by Nunneley² and Peñas³ were not known to Rottino, his own case becomes the thirty-fourth in the series. References to the cases in Rottino's table will not be repeated except that for Vehling,⁴ whose dissertation, available in microfilm, can now be cited more accurately.

Probable examples, which do not qualify for inclusion in Table I because perforation was impending rather than actual, or because it is not clear that the aneurysm was primarily aortic, can be found among studies reported from other points of view. Washburn and Wilbur⁵ described obstruction of the third portion of the duodenum by an aneurysm of the abdominal aorta. The patient was a woman, aged 67, with a large, pulsating, epigastric mass. There had been no blood in the vomitus, but later there was a slight trace of blood in a test meal and occult blood in the stools. Rupture must have been impending in this case. The clinical diagnosis was confirmed when a posterior gastroenterostomy was performed for the relief of obstruction.

In an analysis of the symptoms and signs in a group of twenty-four cases of abdominal aneurysm, Eliason and McNamee¹⁰ found massive hematemesis and melena each mentioned once. Although pain was the predominant symptom in

From the Department of Pathology, University of Michigan.
Received for publication April 18, 1946.

TABLE I. AORTIC ANEURYSM RUPTURING INTO THE GASTROINTESTINAL TRACT

NO.	DATE	AUTHOR	AGE	SEX	PERSISTENT HISTORY LEADING TO ADMISSION	CLINICAL OBSERVATIONS	COURSE	PATHOLOGIC CHANGE
32*	1906	Namulev ²	28	M	Pain in epigastric region	Pulsating tumor below ensiform cartilage	Two months after admission, hematemesis and death	Saccular aortic aneurysm above origin of celiac axis; perforation into left side of anterior portion of duodenum
33	1941	Peñas ³	62	M	Pain in lumbar and right inguinal regions	Tumor mass in umbilical region	Sixteen days after admission, sudden weakness, rapid pulse, hematemesis, unconsciousness, and death in six hours	Massive gastrointestinal hemorrhage; saccular aortic aneurysms arising below superior mesenteric artery rupturing into third portion of duodenum
34	1943	Rottino ⁴	53	M	"Arthritis" of right hip, epigastric pain	Pulsating mass with bruit in epigastrium	Sudden hematemesis, melena, and death in two days	Saccular aortic aneurysm below renal arteries rupturing into third portion of duodenum
35	1943	Howland and Sproffkin ⁶	59	M	Pain in left upper quadrant for six weeks	Albuminuria, then anuria	Sudden "shock" with ashy pallor; death three days after onset of anuria	Saccular aortic aneurysm at level of superior mesenteric artery, compressing left renal vein and rupturing into third portion of duodenum
36	1944	Hiller and Johnson ⁷	76	M	Epigastric pain for five weeks	Occult blood in stools	Found semicomatose with dark red liquid feces in bed; death forty minutes later	Saccular aneurysm 6.5 cm. above aortic bifurcation, rupturing into jejunum 2 cm. below duodenum

37	1944	Morison ⁸	64	F	Aching pain on both sides of abdomen; frequent scalding micturition	Pulsating tender mass to left of umbilicus	After ten weeks, severe hematemesis and death in seven hours	Saccular aortic aneurysm just above inferior mesenteric artery; rupture into third portion of duodenum
38	1944	Pratt-Thomas	31	M	Epigastric pain for three months; collapsed while walking; hematemesis	Visible pulsating mass above and to right of umbilicus	State of "shock"; death in two hours; profuse hemorrhage from rectum	Saccular aneurysm at level of celiac axis and superior mesenteric artery; perforation into duodenum, 20 cm. below pyloric ring; stomach and intestine filled with blood
39	1944	Pratt-Thomas ⁹	48	M	Pain in epigastrium and radiating from lumbar spine; vomiting	Pulsating mass in umbilical region, increasing in size	Died suddenly as gastric tube was about to be passed	Saccular aortic aneurysm immediately below mouths of renal arteries; perforation into third portion of duodenum; stomach and intestine filled with blood
40	1944	Pratt-Thomas ⁹	52	M	Abdominal pain; hematemesis	State of "shock"; melena	Death seven days after hematemesis	Aneurysmal dilatation of aorta 1 cm. below renal arteries; perforation into overlying duodenum; intestine nearly filled with blood
41	1946	Hunt and Weller	47	M	Entered hospital for pain in right knee	Septic arthritis, acute psychosis	Hematemesis, death in five hours	Saccular aortic aneurysm 4.5 cm. below superior mesenteric artery; rupture into third portion of duodenum

*Numbered in sequence with cases collected by Rottino.¹

the group as a whole, reference is made to one patient who had very little pain but did have massive hematemesis from rupture of an aneurysm of the *celiac axis* into the jejunum. Death occurred twenty-four hours after the onset of hemorrhage. This case and one other, attributed to the celiac axis, are excluded from Table I.

Scott¹¹ included lesions of any abdominal artery in his report of ninety-six cases of abdominal aneurysm. "Massive gastrointestinal hemorrhage followed rupture into the duodenum in one patient." In his table a second patient is recorded as having hemorrhage into the duodenum following rupture. Whether one or both of these were aortic aneurysms is not stated.

A brief account of our case follows.

CASE REPORT

I. B., No. 483037, was an unmarried Swedish bricklayer, aged 47. He was admitted to the University of Michigan Hospital with a painful left knee as his chief complaint. Physical evidences of septic arthritis were present and bone destruction was found roentgenographically. The patient developed an acute psychosis and a reliable history could not be obtained. However, he referred the onset of pain to a period about one month prior to admission. Venereal infection was denied, but exposure six weeks before entry was admitted. Serologic test of the blood (Kahn) was negative on two occasions. The gonococcal complement fixation test of the blood serum was strongly positive. The patient was given sulfathiazole, and three operative procedures for drainage of the left knee were carried out. On the third postoperative day, at 5 A.M., the patient had a sudden hemorrhage from the mouth, amounting to about 300 c.c. of fluid and clotted blood. A medical consultant suggested pulmonary infarction, but roentgenograms of the chest were negative. None was made of the abdomen. At 10:15 A.M. of the same day, the patient had a second hemorrhage and expired.

Autopsy.—At autopsy (A-420-AS), the stomach, duodenum, and entire small bowel were found to be filled with a jellylike blood clot forming a cast of the lumen. In the transverse segment of the third portion of the duodenum there was a small, irregular opening which communicated with a firm, somewhat elastic, retroperitoneal mass. After removing the duodenum and aorta together, this mass was found to be a saccular aneurysm protruding from the right anterolateral surface of the abdominal aorta. The sac measured 6 cm. vertically, 4.5 cm. transversely, and 3.5 cm. ventrodorsally. Its upper border was 4.5 cm. below the orifice of the superior mesenteric artery and its lower border 2 cm. above the iliac bifurcation. The mouth of the sac lay to the right of the inferior mesenteric artery and measured 2.5 by 2 centimeters. The wall of the sac was composed of thick fibrous and calcareous laminae (Figs. 1 and 2). The remainder of the abdominal aorta showed thickening of the wall, loss of elasticity, widening of the lumen, and numerous yellowish-gray, elevated, hyaline plaques against a grayish-white intima. There were also areas of atheromatous "ulceration," but the gross features of syphilitic aortitis were not found.

Sections of all organs were examined microscopically. The heart showed atherosclerotic changes of the coronary arteries and at the bases of the aortic cusps. In the myocardium there were scattered interstitial infiltrations of mononuclear cells, in part eosinophiles, which were thought to be due to the use of sulfathiazole.

The aorta was examined in sections from several levels. In the upper portion of the thoracic aorta, atheromatous changes were of but slight degree. There was a very moderate increase in the blood vessels of the adventitia, about some of which there was a slight lymphocytic infiltration. In the abdominal aorta there were very marked atheromatous lesions of the intima, with deposition of cholesterol and calcareous plaques. The media showed areas of necrosis with fragmentation and ultimate loss of elastic fibers. In the adventitia there were infiltrations of



Fig. 1.—The abdominal aorta has been opened approximately along the mid-dorsal line. The mouth of the aneurysmal sac is shown to the right of the opening of the inferior mesenteric artery. The adherent duodenum is largely concealed by the sac of the aneurysm.

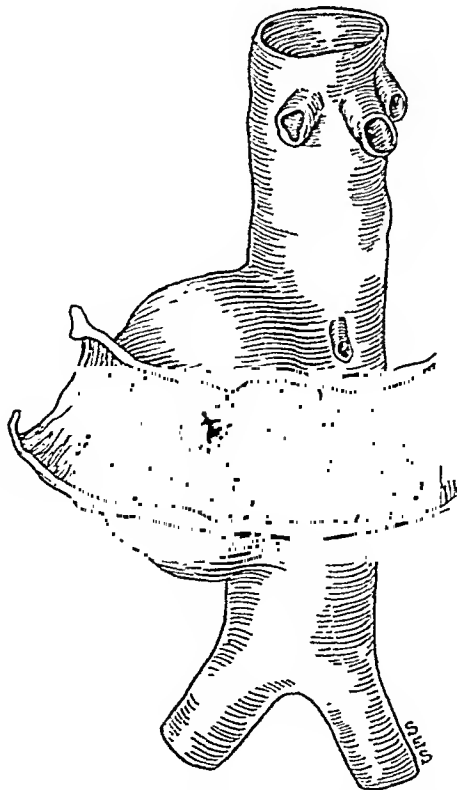


Fig. 2.—This schematic drawing, prepared from a photograph and sketch made at the time of the autopsy, shows more clearly the anatomic relations of the aneurysm. Rupture into the duodenum occurred at the summit of the convexity of the anterior wall of the sac.

lymphocytes and plasma cells, but the changes found were not such as to justify a diagnosis of syphilitic aortitis.

Near the point of perforation of the aneurysm into the duodenum there were organizing, fibrinous peritonitis and necrosis and leucocytic infiltration of the mucosa.

A section of synovial membrane from the left knee showed active chronic pyogenic inflammation with numerous plasma cells. This was considered to be fully compatible with the clinical impression of gonococcal arthritis.

The pathologic diagnoses were: large saccular aneurysm of the abdominal aorta, with rupture into the third portion of the duodenum and massive hemorrhage into the bowel; hematemesis, with aspiration of blood into the lungs; advanced aortic atherosclerosis; organizing fibrinous peritonitis of the duodenum; coronary atherosclerosis; old epicarditis; subepicardial fatty atrophy of the myocardium; left ventricular myocardial hypertrophy; interstitial myocardial infiltrations of large mononuclear cells and eosinophiles (sulfathiazole?); pulmonary congestion and edema; beginning terminal lobular pneumonia; degenerative fatty infiltration of the liver and kidneys; septic arthritis of the right knee (gonococcal?); cholelithiasis.

DISCUSSION

Incidence as to Sex and Age.—This augmented series adds to the earlier emphasis upon the greater liability of men to this syndrome. With thirty-five of forty-one examples in men, a 6:1 ratio is found. The range in age remains unaltered, from 20 to 81 years. While the distribution by decades is fairly uniform between these extremes, correction for total number living would show an increasing incidence beginning with the sixth decade. It can be due only to chance that for four of the thirty-eight patients the age was 28 years. Yet the occurrence of eight cases in the six-year period between 27 and 32 years-of-age emphasizes the importance of this syndrome in a comparatively young group.

Location of the Aortic Aneurysm.—In sixteen cases the level at which the aortic aneurysm had developed was not stated with sufficient exactness to be used in tabulation. Moreover, the large size of many of these aneurysms in comparison to the small distances between successive aortic branches must have rendered exact localization impossible in many cases. Locations were specified as follows: above celiac axis, two cases; at celiac axis, three; above superior mesenteric artery, one; at superior mesenteric artery, one; below superior mesenteric artery, five; above renal vessels, one; below renal vessels, six; below inferior mesenteric artery, two; lower abdominal aorta, one; above aortic bifurcation, three.

Location of Rupture Into Gastrointestinal Tract.—As found by Rottino, the third portion of the duodenum is the portion of the gastrointestinal tract into which perforation of an abdominal aortic aneurysm occurs most frequently. This site was specified, or could be deduced, in twenty-nine of the forty-one cases. In two others, perforation was into the second portion of the duodenum, and in two into the duodenum, without specification as to the portion. Of the remaining cases, five showed perforation into the stomach, two into the jejunum, and one into the small bowel, with the region unspecified. The reasons for the preponderance of perforation into the third portion of the duodenum are anatomic,

depending in part upon the extensive area in which this portion of the duodenum is in relationship to the anterior aortic wall and also upon its firm fixation to the aorta, since the duodenum is retroperitoneal in this portion.

CLINICAL MANIFESTATIONS

The syndrome produced by the rupture of an abdominal aortic aneurysm into the gastrointestinal tract combines the features of abdominal aneurysms in general with those of hemorrhage into the alimentary tract. An accurate ante-mortem diagnosis may be possible in spite of the rarity of the condition.

For the basic clinical picture of abdominal aortic aneurysm, Kampmeier¹² gave the following as important diagnostic points: presence of an abdominal tumor (60 per cent of all cases); expansile pulsation of the tumor (in 98 per cent of those with tumors); roentgenologic evidence of a calcified abdominal mass, of vertebral erosion, or of an indefinite soft tissue mass (confirming evidence being found by this method in 75 per cent of thirty-two cases in which it was used). With any abdominal aortic aneurysm, death is usually due to hemorrhage, whether the aneurysm is saccular or dissecting. Sometimes death is almost instantaneous, but it may be delayed for hours or days. Lipshutz and Chodoff¹³ added to the general picture of abdominal aneurysm the following, as evidence that rupture had occurred: vascular crisis and a state of shock, a high leucocyte count, moderate elevation of diastase content of the urine.

All of the diagnostic criteria summarized by Kampmeier and by Lipshutz and Chodoff apply to the cases of aneurysms in which perforation into the gastrointestinal tract is impending or has occurred. The tumor mass is usually epigastric in position and it is frequently expansile and pulsating. Pain is the chief complaint and may be abdominal or in the lumbar region. Hematemesis and melena are usual terminal features but, as with thoracic aortic aneurysms, there may be a premonitory seepage of blood for days or weeks before the final exsanguinating hemorrhage. This may be discovered through blood-tinged vomitus or as occult blood in the stools. Death may occur immediately, or after a variable interval, following the copious hematemesis or escape of fresh blood from the rectum which completes the diagnostic picture. The report by Manson¹⁴ is typical. "I was called to a passenger train on June 18, 1936, to attend a man who was seriously ill. This man was found to be lying on his back in a first-class lavatory with his trousers down, in a mass of blood and feces. He was blanched and unconscious, and at first sight seemed to be dead." A pulsating tumor was felt in the epigastrium. This patient died five days later and was found to have a saccular aneurysm of the abdominal aorta, which had ruptured into the duodenum. In our own case, hematemesis marked the occurrence of rupture.

There are additional features which may lead the clinician away from the correct diagnosis unless their logical association with this syndrome is recognized. For instance, a high leucocyte count appears to be a constant feature during the period between actual rupture and death. Again, a detailed history of "indi-

gestion" may seem to point so clearly to peptic ulcer that the physical and roentgenographic evidences of aneurysm may be overlooked. The frequency with which an elevated value for urinary diastase will be found has not yet been established but deserves further study. Impairment of renal function has been observed in many instances and depends chiefly upon interference with one or both renal arteries. In the case described by Howland and Sprofskin,⁶ in which there was terminal anuria, the mouths of the renal arteries were included in the aneurysmal sac and a thrombus extended into the right renal artery.

SUMMARY

With the new case, which is reported in this paper, forty-one examples of rupture of an aneurysm of the abdominal aorta into some portion of the gastrointestinal tract are known to be available in the literature. In 71 per cent, rupture was into the third portion of the duodenum. The condition has been six times more frequent in men than in women. While the ages were widely distributed, the occurrence of eight cases between 27 and 32 years-of-age indicates the importance of this condition in relatively young patients. The resulting syndrome combines the features of abdominal aneurysm with those of profuse hemorrhage into the gastrointestinal tract. Hematemesis, often with abundant hemorrhage from the rectum, usually marks the onset of the terminal phase.

REFERENCES

1. Rottino, A.: Aneurysm of Abdominal Aorta, With Rupture Into the Duodenum. Case Report and Review of the Literature, *AM. HEART J.* 25: 826, 1943.
2. Nunneley, F. P.: Aneurysm of the Abdominal Aorta, London, 1906, Baillière, Tindall & Cox, 121 pp.
3. Peñas, M. D.: A Rare Cause of Fatal Haematemesis (Rupture of Aneurysm of Abdominal Aorta Into Duodenum), *U. S. T. J. Med.* 1: 303, 1941.
4. Vehling, Carl: Perforation der Aorta in den Digestionstractus, Inaugural Dissertation, Erlangen, 1878, 40 pp.
5. Washburn, R. N., and Wilbur, D. L.: Obstruction of the Duodenum Produced by Aneurysm of the Abdominal Aorta, *Proc. Staff Meet., Mayo Clin.* 11: 673, 1936.
6. Howland, E. S., and Sprofskin, B. E.: Saccular Aneurysm of the Abdominal Aorta. Report of a Case With Terminal Anuria and Rupture Into the Duodenum, *Am. J. M. Sc.* 206: 363, 1943.
7. Hiller, G. I., and Johnson, R. M.: Abdominal Aortic Aneurysm. Rupture Into the Jejunum Preceded by Occult Blood in the Stool, *Am. J. M. Sc.* 207: 600, 1944.
8. Morison, J. E.: Rupture of Aortic Aneurysm Into the Duodenum, *Brit. M. J.* 2: 244, 1944.
9. Pratt-Thomas, H. R.: Aneurysm of the Abdominal Aorta With Rupture Into the Duodenum. Report of Three Cases, *Am. J. Clin. Path.* 14: 405, 1944.
10. Eliason, E. L., and McNamee, H. G.: Abdominal Aneurysm. A Report of Twenty-Four Cases, *Am. J. Surg.* 56: 590, 1942.
11. Scott, V.: Abdominal Aneurysms. A Report of Ninety-six Cases, *Am. J. Syph., Gonorr. & Ven. Dis.* 28: 682, 1944.
12. Kampmeier, R. H.: Aneurysm of the Abdominal Aorta. A Study of 73 Cases, *Am. J. M. Sc.* 192: 97, 1936.
13. Lipshutz, B., and Chodoff, R. J.: Diagnosis of Ruptured Abdominal Aortic Aneurysm. Report of a Case, *Arch. Surg.* 39: 171, 1939.
14. Manson, J. S.: Rupture of Aorta Into Duodenum, *Brit. M. J.* 1: 121, 1937.

AN AURICULAR DIASTOLIC MURMUR WITH HEART BLOCK IN ELDERLY PATIENTS

DAVID A. RYTAND, M.D.
SAN FRANCISCO, CALIF.

IN NINE elderly but ambulatory patients with varying degrees of auriculo-ventricular block, a blowing murmur was heard at the cardiac apex during ventricular diastole. Phonocardiograms recorded simultaneously with electrocardiograms revealed in each case the vibrations of a murmur, as distinguished from the abrupt auricular sounds so often observed in complete block, and showed the relationship of the murmur to auricular activity. At times, the usual short auricular sounds were also present.

Mitral stenosis did not appear to be present. Calcification of the mitral annulus fibrosus was found in four cases, but this lesion seems not to alter the cardiodynamics as does mitral stenosis and fails to produce an auricular (pre-systolic) murmur when auriculoventricular conduction is normal.¹

The purposes of this paper are to report the observations and to discuss the mechanisms which might be responsible for the production of the murmur.

CASE REPORTS

Cases 1 through 4, with calcification of the mitral annulus fibrosus, are the same as those reported in more detail elsewhere.¹ Cases 5 through 9, without calcification, have not been reported before.

CASE 1.—A frail woman 74 years of age, with no history of rheumatic fever, was found to have moderate congestive heart failure and complete heart block. At times, the latter was replaced by 2:1 block and even sinus rhythm with a P-R interval of 0.19 to 0.21 second, but usually the block was complete. Left bundle branch block was occasionally found, and auricular fibrillation complicated complete block for two months. The arterial pressure varied around 200/90. Improvement followed the use of digitalis and diuretics, so that the patient was ambulatory most of the time. She died at the age of 79 years of cerebral vascular disease; necropsy was not permitted. During the period in which the observations recorded below were made, signs of heart failure were virtually absent. The heart did not appear enlarged on physical examination. X-ray examination, however, revealed slight enlargement; the left auricle was not prominent. A nearly complete ring of calcification in the region of the mitral annulus fibrosus was seen fluoroscopically and recorded on films.

There was a loud, coarse murmur during ventricular systole, best heard along the lower left sternal border and transmitted to the apex, aortic area, and carotid arteries. There was no thrill. With complete block, the first heart sound varied in intensity and a blowing murmur in ventricular diastole was heard at the apex. The murmur was enhanced in the left lateral recumbent position. Its position in diastole varied, depending upon the time of auricular activity. The murmur was not heard more than twice in any given diastolic period. When it occurred early in diastole, it was obviously louder than when it occurred later (Fig. 1).

From the Department of Medicine, Stanford University School of Medicine.
Received for publication March 23, 1946.

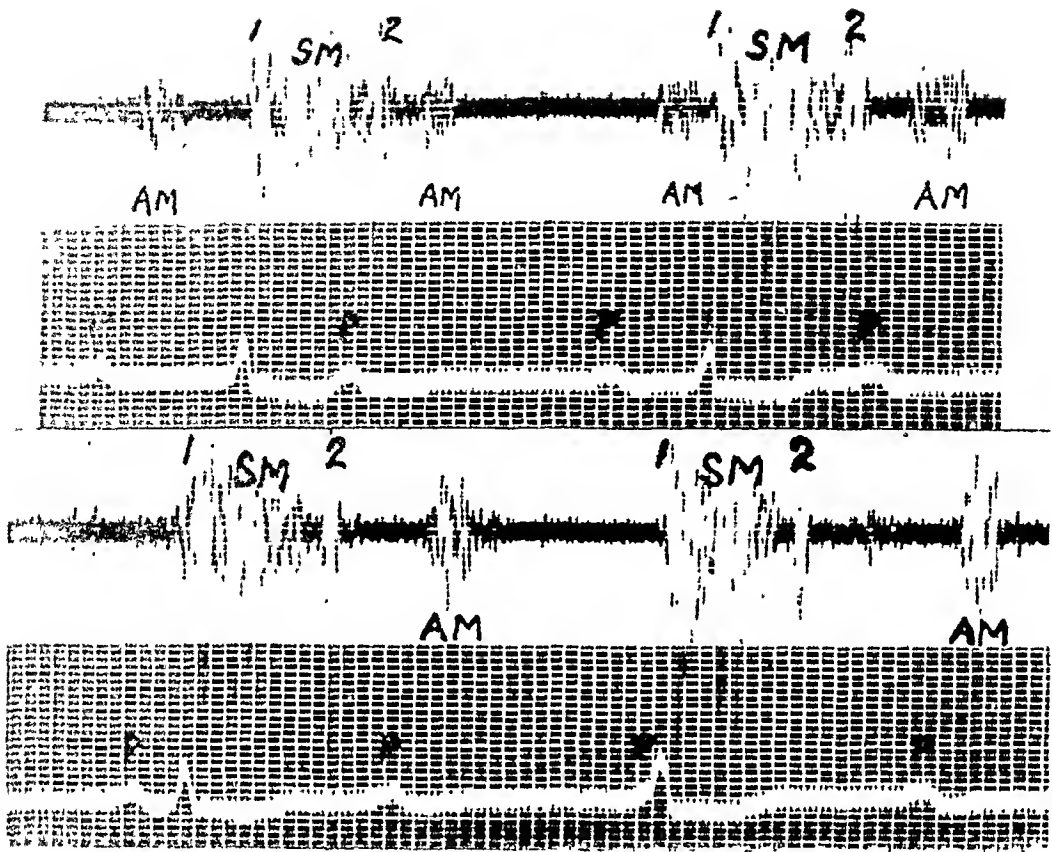


Fig. 1—Case 1. Simultaneous records of heart sounds at the apex and electrocardiogram. Complete A-V block. Time marking in all figures, 0.01 and 0.20 second. The first and second heart sounds are designated 1 and 2; the murmur of ventricular systole, SM; the auricular murmur, AM. Vibrations of the auricular murmur are smaller both early and late in ventricular diastole (upper strip) than at intermediate times (lower strip) and are not recognizable as such with normal P-R intervals (0.17 second in first cycle of lower strip). Small unlabeled vibrations are artefacts. Upper and lower strips are consecutive.

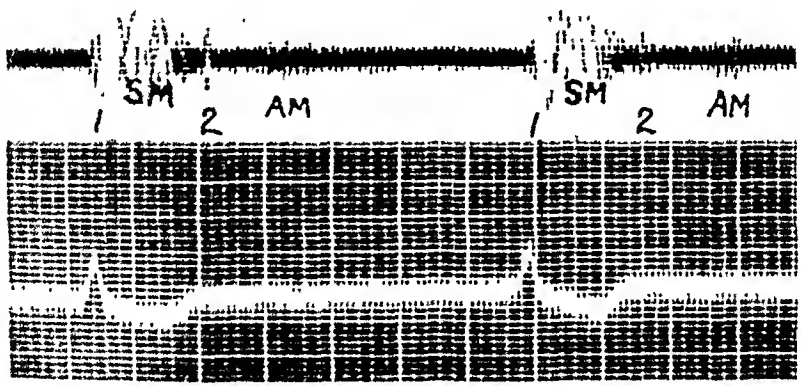


Fig. 2.—Case 1. Same as shown in Fig. 1, but during auricular fibrillation. Small vibrations of murmur, AM, are related to the second heart sound.

When 2:1 block was present, the murmur was audible only in the blocked auricular cycle and not well recorded in the conducted one (P-R interval, 0.24 second; preceding R-R cycle, 1.44 second). In the presence of auricular fibrillation, it was faintly audible and recorded early in diastole (Fig. 2). It was not heard during the short periods of sinus rhythm, but unfortunately we were not then aware of the possibility of its existence.

CASE 2.—Dyspnea and angina pectoris in a husky man 68 years of age led to the discovery of calcification in the mitral annulus fibrosus. There was no history of rheumatic fever. After a period of prolonged conduction time, the P-R interval fell to 0.18 second. Digitalis administration was followed temporarily by complete block, then 3:2 block; observations noted in the next paragraph began at this time. Later, even without digitalis, the P-R interval remained fairly constant at 0.30 second. A year later, auricular fibrillation with slow but irregular ventricular response appeared and persisted. Congestive heart failure, starting about the same time, finally led to the patient's death two years after the first examination.

The arterial pressure was 135/90. There were no signs of congestive heart failure. The heart was only slightly enlarged on x-ray examination and the left auricle was not prominent. There was a loud, rough murmur with ventricular systole, loudest at the base but also heard at the apex and over the carotid arteries. There was no thrill. With complete block, a rough, blowing murmur at the apex was audible during ventricular diastole, with behavior similar to that of the murmur described in Case 1. The first heart sound varied in intensity (Fig. 3). When 3:2 block was present, the murmur was not heard with the first of the conducted cycles (P-R interval, 0.24 second), and with such cycles its vibrations were scarcely visible in phonocardiograms; under these conditions the preceding R-R cycle length was 1.38 seconds. With prolonged conduction time (P-R interval, 0.30 second), the murmur was a presystolic one (Fig. 4).

With congestive failure and auricular fibrillation, the left auricle and the heart became dilated. The murmur then became confined to early diastole (Fig. 5), was fainter than when associated with auricular activity, and could not be heard with the patient sitting up.

CASE 3.—An obese woman 68 years of age was found in 1939 to have complete heart block, which persisted until she died of myocardial infarction in 1942. The observations recorded below were made in 1941, when she was seen because of postural vertigo and when she was somewhat dyspneic but ambulatory. There was no history of rheumatic fever. The arterial pressure was 270/110, and peripheral arteriosclerosis was marked. There were no physical signs of congestive heart failure, although there was marked cardiac enlargement. Radiologic study revealed calcification of the mitral annulus fibrosus. The left auricle was not unduly prominent.

A thrill at the base accompanied a loud systolic murmur which was transmitted to the apex and into the carotid arteries. The first heart sound varied in intensity. A soft, blowing murmur was heard at the apex during ventricular diastole; it behaved quite like the similar murmur described in Case 1 (Fig. 6).

At necropsy, the heart weighed 420 grams. The aortic, pulmonic, and tricuspid valves were normal. A band of calcification 1 cm. thick and 9 cm. in circumference encircled the mitral valve in the annulus fibrosus without obstructing the orifice. There was some calcification and distortion of the mitral leaflets near their base, but their free edges and chordae tendineae were normal. There was very slight, diffuse endothelial thickening in the left auricle, without striking enlargement of that chamber. A myocardial infarct was present, and the coronary arteries were diffusely narrowed. Aortic atherosclerosis was marked. Firm masses of calcified fibrous tissue nearly occluded the proximal portions of the innominate and left carotid arteries.

CASE 4.—In 1936, a very small woman 73 years of age developed dyspnea while at the Laguna Honda Home. Study of this symptom led to the discovery of complete heart block; moderate congestive heart failure was present then, but not later.

Examinations subsequent to 1942 revealed advanced peripheral arteriosclerosis. The arterial pressure was 220/70. The heart was somewhat enlarged, its rhythm was regular, and the ventricular rate was 46. There was a rough systolic murmur, faint at the apex, moderate at the left sternal border, and not reaching the carotid arteries.

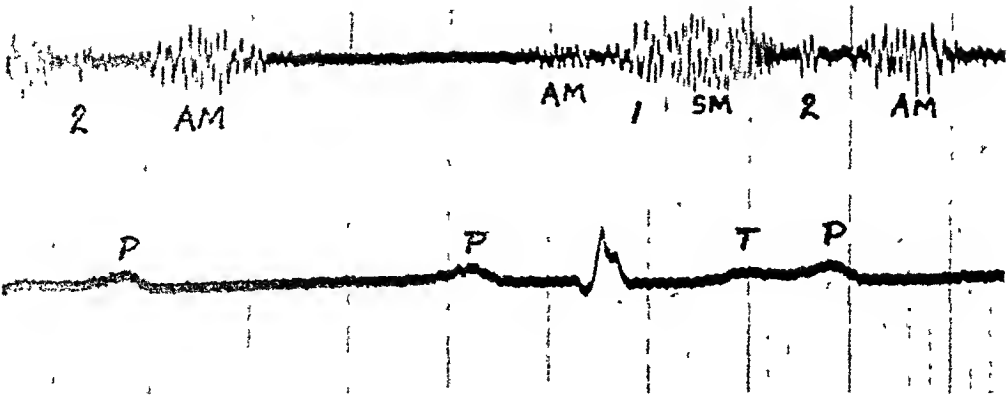


Fig. 3 -Case 2 Same as shown in Fig. 1. Complete A-V block. Vibrations of the auricular murmur, AM, are greater early in diastole.

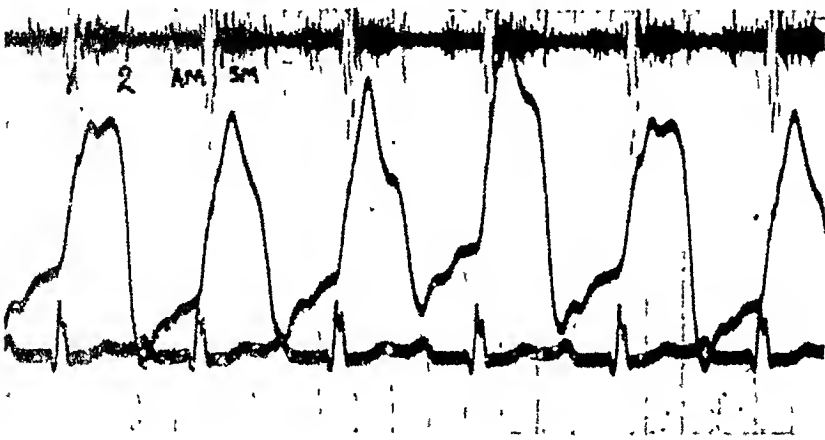


Fig. 4--Case 2. Simultaneous records of apical heart sounds, apex beat, and electrocardiogram. Sinus rhythm; P-R interval, 0.30 second.

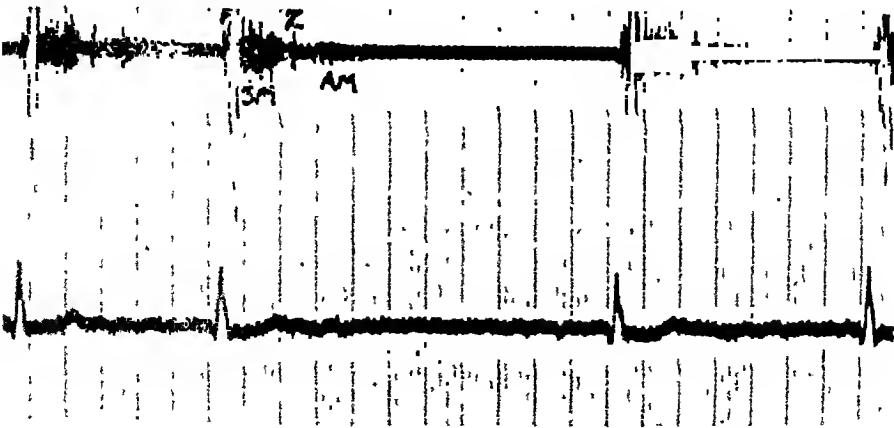


Fig. 5.—Case 2. Same as shown in Fig. 1 but during auricular fibrillation.

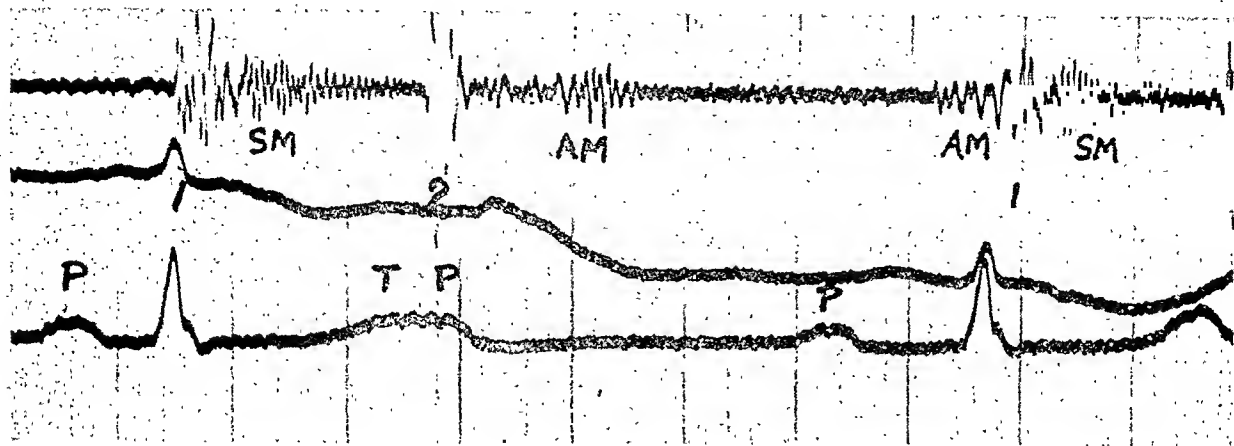


Fig. 6.—Case 3. Same as shown in Fig. 1. Complete A-V block. (Ignore the irregular central tracing.) There is no auricular murmur with the first P wave, P-R interval, 0.20 second, although one is present with a P-R interval of 0.30 second at the end of another diastole of equal length.

The first heart sound varied in intensity. Systole occasionally contained a loud click. At the apex, a short, blowing murmur was heard at variable times in diastole. It was loud during early diastole but became faint by mid-diastole. It was never heard late in diastole, but sometimes double auricular sounds were then noted. This murmur was loudest with the patient recumbent or in the left lateral position, but was also present in the upright position. Very recently the murmur sounded rumbling rather than blowing. It was never heard more than once in any one cycle. Phonocardiograms (Figs. 7 and 8) confirmed these signs, showed their relation to auricular activity, and also revealed a partially split first sound.

Careful radiologic study in 1942 and 1944 failed to demonstrate calcification of the mitral annulus fibrosus. However, in October, 1945, that lesion was shown. The left auricle was then thought to be prominent, although enlargement had not previously been noted. The heart itself was moderately enlarged as in earlier examinations.

Electrocardiograms always showed complete heart block and left axis deviation.

CASE 5.—This man was 40 years of age when he first visited Stanford outpatient clinic in 1923 because of pain which was found to be caused by osteoarthritis. There was no history of rheumatic fever. The heart was normal on physical examination and fluoroscopy. The arterial pressure was 110/80. An electrocardiogram showed only auricular premature beats.

Repeated examinations were negative as late as 1937, when the arterial pressure was 140/90. In 1941 the pressure was 160/100; the heart was regular and not enlarged, and there was a loud systolic murmur over the precordium, loudest along the left sternal border but not reaching the carotid arteries.

In March, 1942, he visited the cardiac clinic because of pain in the chest which was unrelated to effort. The heart rate was 53 and the rhythm was regular. There was a loud apical systolic murmur. During diastole there was also heard at the apex a short, rather low-pitched murmur, which was quite loud in the left lateral recumbent position. There were no signs of congestion. The arterial pressure was 140/80. An electrocardiogram showed sinus bradycardia with prolonged conduction time (P-R interval, 0.51 second) but no other abnormalities. Careful radiologic study including fluoroscopy and roentgenkymograms failed to reveal intracardiac calcification. The heart was not enlarged and the left auricle was not dilated. In 1943 complete heart block was present; the ventricular rate was 36 and the first heart sound varied in intensity. Associated with auricular activity, a blowing but rather low-pitched murmur was heard at the apex in variable phases of ventricular diastole. The murmur was loudest when it came early in diastole.

In 1944, the patient was requested to return for reexamination. He was then 61 years old and was working as a janitor. He appeared to be well and showed no signs of congestive heart failure. The heart rate was 27 and the rhythm was regular. There was a loud, harsh murmur

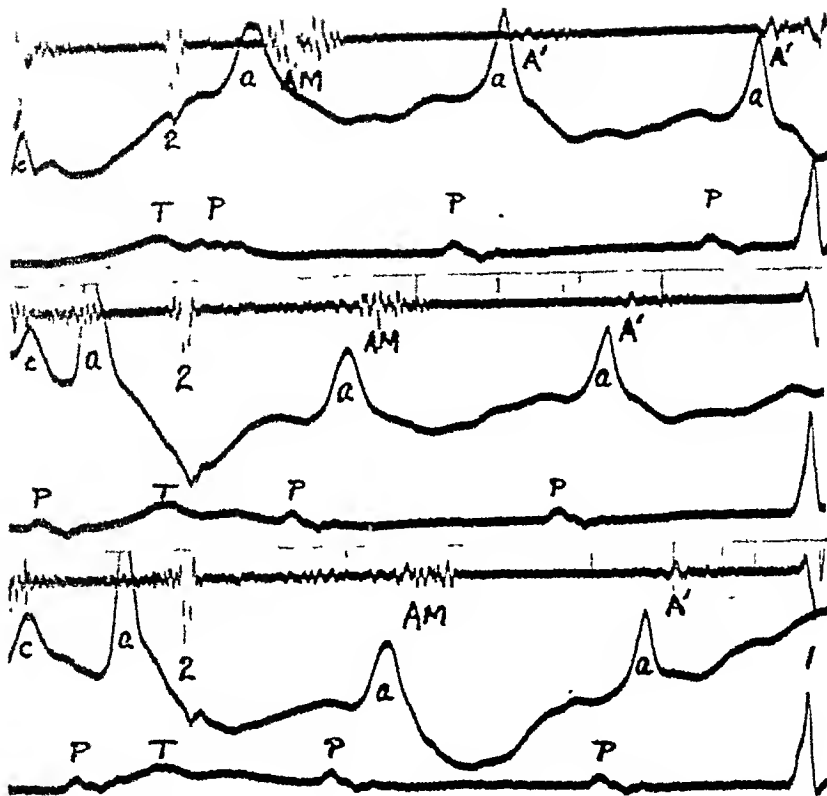


Fig. 7—Case 1. Simultaneous records of the heart sounds at the apex, jugular pulse, and electrocardiogram. Complete A-V block. Taken from a continuous tracing, each strip represents one ventricular cycle, from above downward, they are first, fourth, and third chronologically. Jugular *a* waves associated with occasionally audible auricular double sound vibrations, *A'*, are no broader or taller than those with auricular murmur, *AM*; *a* waves during ventricular systole are very tall. The auricular murmur follows the *a* wave

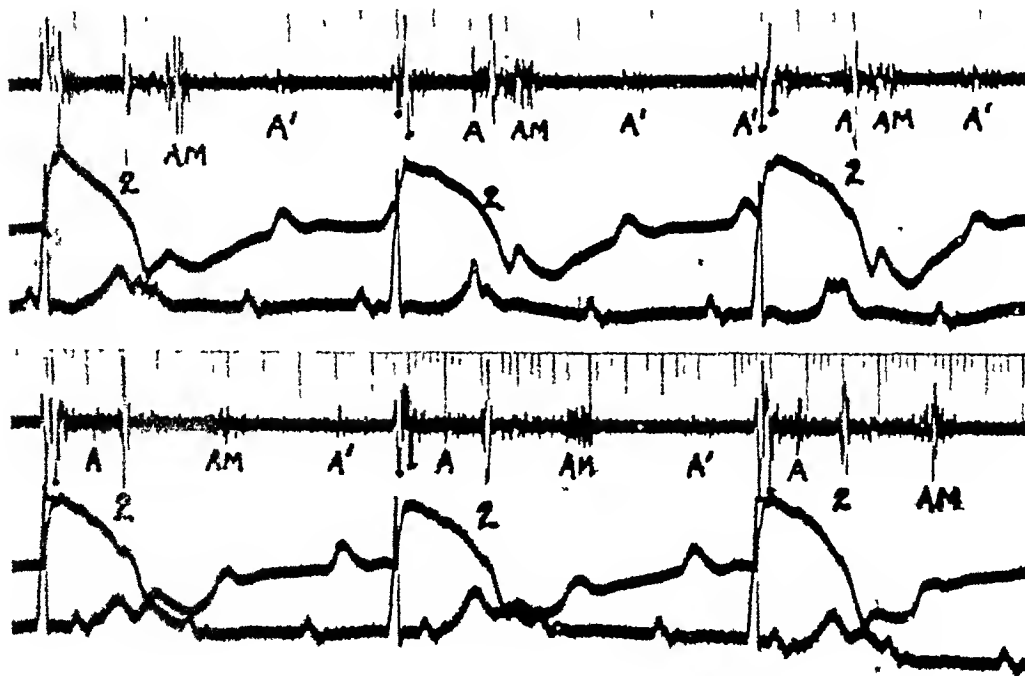


Fig. 8—Case 1. Simultaneous records of the heart sounds at the apex, apex beat, and electrocardiogram. Complete A-V block. Taken from a continuous tracing, upper and lower strips were separated by two cycles. Dots indicate variable intensities of the partially split first heart sound. In the second and third cycles, a P wave just before the second heart sound is associated with an auricular sound, *A*, in ventricular systole as well as with an auricular murmur, *AM*. The latter follows the second sound by 0.06 to 0.08 second. At times, as in the second cycle, vibrations following the auricular sound during ventricular systole resemble those of a murmur.

at the apex and especially at the left sternal border during ventricular systole. A third heart sound was audible at the apex and was followed immediately by a blowing murmur. Auricular sounds were barely audible late in diastole (Fig. 9). An electrocardiogram showed 2:1 A-V block.

CASE 6.—A man 59 years of age had visited the cardiac clinic for two years because of angina pectoris and dyspnea on effort. He had a history of six attacks of gonococcal urethritis with arthritis, three of them under observation. There was no history of rheumatic fever.

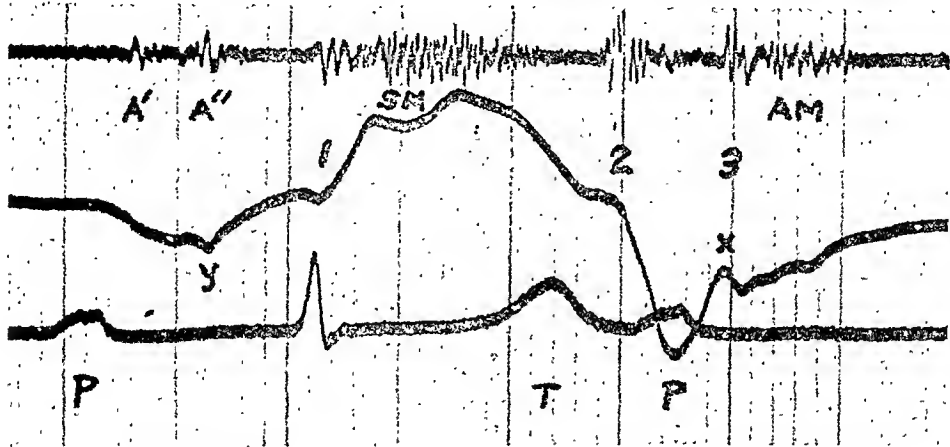


Fig. 9.—Case 5. Simultaneous records of heart sounds at the apex, apex beat, and electrocardiogram, 2:1 A-V block. Upper strip, sensitized paper moving at 75 mm. per second; lower strip, at 25 mm. per second. The first and second components of auricular sounds with the conducted P wave are designated A' and A''; AM is the murmur initiated by the third heart sound, 3. The latter coincides with the thrust *x* of the apex beat, A'' with the oppositely directed thrust *y*. With the second and sixth P waves in the lower strip, sound vibrations appear less like those of murmur than like those of double sounds; the second components of these coincide with additional waves in the apex beat.

When the patient was first seen, the heart rate was 60 and the rhythm was regular. No murmurs were noted in the clinic record. The arterial pressure was 180/105. An electrocardiogram showed sinus rhythm with P-R intervals of 0.32 second. When the heart sounds were recorded (Fig. 10) in 1942, there was transient complete heart block but no signs of congestive failure. A faint, blowing apical murmur was noted early in diastole. Radiologic study showed the heart and left auricle to be normal in size. Intracardiac calcification was specifically looked for but was not found.

At the present time he is in the San Francisco Hospital with moderate congestive failure and incomplete heart block. A blowing apical murmur was heard at varying times, especially in early diastole; it was present with the patient in an upright position as well as in a supine; no other signs of mitral stenosis were found.

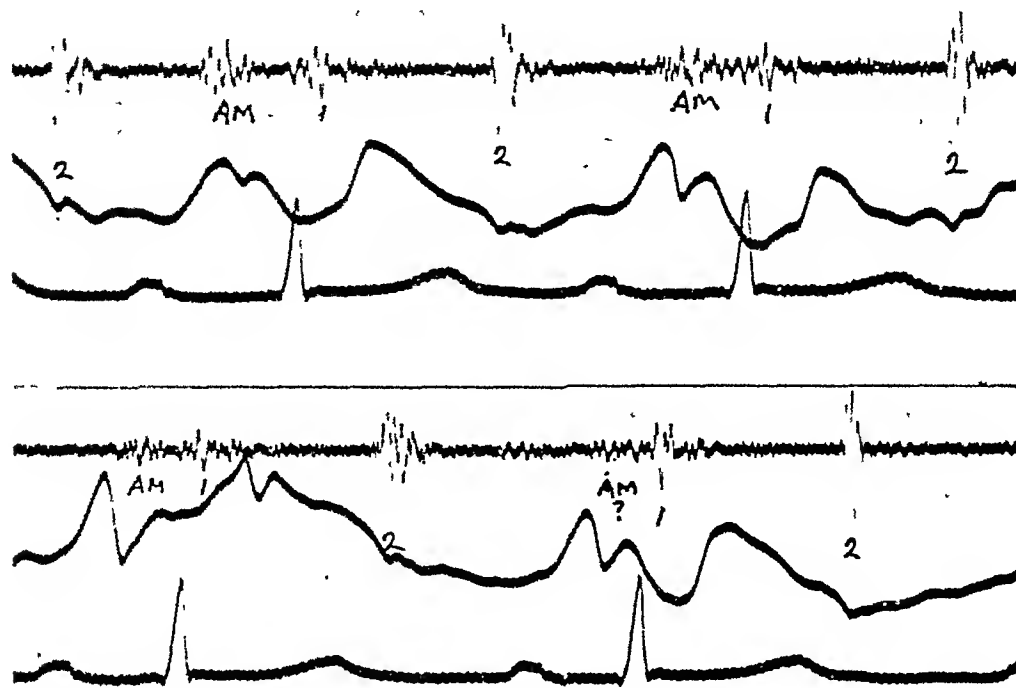


Fig. 10.—Case 6. Simultaneous records of the heart sounds at the apex, jugular pulse, and electrocardiogram. Complete A-V block. Upper and lower strips are consecutive. The auricular murmur, AM, was audible when the P wave began 0.16 to 0.18 second after the start of the second heart sound. It was probably inaudible when that interval was 0.22 to 0.28 second. No systolic murmur is recorded.

CASE 7.—A healthy woman 70 years of age consulted a surgeon in 1943 because of ulcers which complicated varicose veins. A murmur was heard in the course of a general examination. There was no history of rheumatic fever.

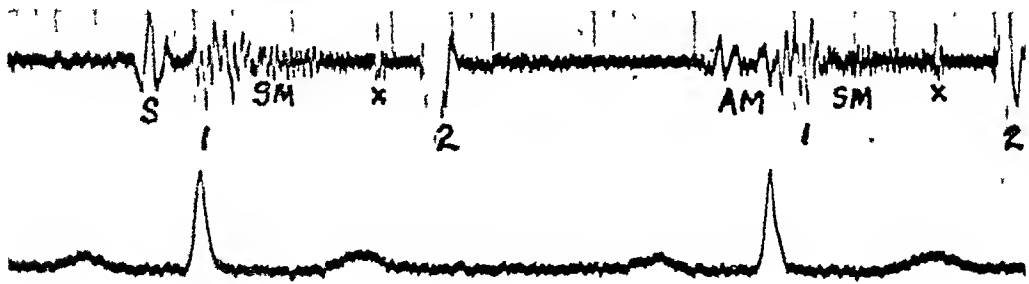


Fig. 11.—Case 7. Simultaneous records of heart sounds at the apex and electrocardiogram. Sinus rhythm, P-R interval, 0.26 second. The usual auricular murmur, AM, is occasionally replaced by vibrations of a sound, S. There is also an extra sound, x, during ventricular systole.

The heart was not enlarged, its rate was 76, and its rhythm was regular. There was a presystolic blowing apical murmur, as well as a loud, rough systolic murmur over the entire precordium (Fig. 11). There were neither signs nor symptoms of congestive failure. Peripheral arteriosclerosis was moderate. Arterial pressure was 200/100. The electrocardiogram revealed only prolonged conduction time (P-R 0.26 second). No calcification could be found within the heart on fluoroscopy or in x-ray films. The heart size was at the upper limits of normal; there was no auricular dilatation.

CASE 8.—A man 53 years of age requested a cardiac examination. He had had chorea repeatedly over three years as a child, and was first told of a murmur when 21 years of age. More recently, hypertension and weakness appeared, and a month before he was seen here there had been an episode resembling pulmonary infarction.

The heart was of normal size, the rhythm was regular, and the rate was 60. There was a blowing presystolic murmur (Fig. 12) and a soft systolic murmur at the apex. The first sound at the apex was split and was not loud. Early diastole was clear. Arterial pressure was 160/100 but fell to 140/85 after a few days in bed. There were no signs or symptoms of congestive failure, and peripheral arteriosclerosis was slight. An electrocardiogram showed prolonged conduction time (P-R interval, 0.32 second) and abnormal T waves, without axis deviation. Careful radiologic study revealed no general cardiac or left auricular enlargement, and no intracardiac calcification.

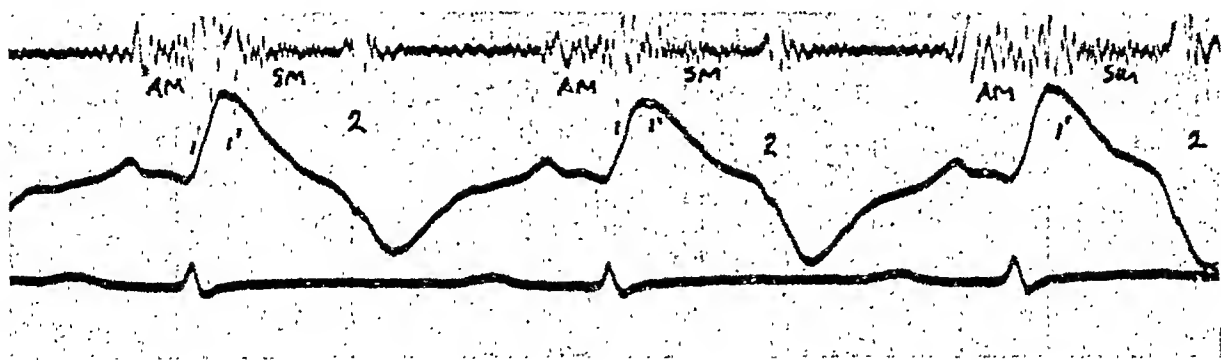


Fig. 12.—Case 8. Simultaneous records of the heart sounds at the apex, apex beat, and electrocardiogram. Sinus rhythm, P-R interval 0.32 second. The auricular murmur, AM, often starts abruptly. The first heart sound is usually split, 1, 1'. The systolic murmur, SM, is inconspicuous.

CASE 9.—A woman 60 years of age gave a history of some sort of rheumatism in childhood. Starting at the age of 24 years, she became progressively more crippled by rheumatoid arthritis. About this time she began to have attacks of paroxysmal tachycardia which became temporarily worse in 1944 when she entered Lane Hospital.

Examination showed extensive rheumatoid arthritis and emaciation but no congestive failure. The arterial pressure was 190/110. There was relatively slight peripheral arteriosclerosis. The heart was moderately enlarged. Its rhythm was disturbed by auricular and ventricular premature beats and by paroxysms of auricular tachycardia. The first heart sound was widely split; there was a loud, blowing murmur between its two elements, best heard at the apex. Diastole was clear; the few presystolic vibrations seen in the sound records (Fig. 13) are probably not a murmur. Electrocardiograms showed P-R intervals of 0.16 to 0.18 second and a wide QRS complex with deep, broad S waves in Lead I. Simultaneous records of the electrocardiogram, heart sounds, and carotid pulse confirmed the presence of right bundle branch block. Radiologic study revealed a moderately enlarged heart but no auricular dilatation or intracardiac calcification.

During an attack of auricular tachycardia, the electrocardiogram showed Wenckebach's periods. Simultaneous records of the heart sounds at the apex (Fig. 13) revealed vibrations of a murmur in the cycles having long P-R intervals and especially in with those with blocked P waves. The murmur was not recognized on auscultation.

A year later an excessive dose of digitalis was followed by an arrhythmia in which the P waves and RS-T complexes were occasionally dissociated, each having a normal rate. When the P wave appeared shortly after the T wave, there was usually a longer-ensuing pause. In these slower cycles, an early short, blowing diastolic murmur was occasionally heard at the apex. This was confirmed at the San Francisco Hospital, but further phonocardiograms could not be obtained. No signs of mitral stenosis were found. The heart was enlarged, and the radiologists believed the left auricle was overly dilated.

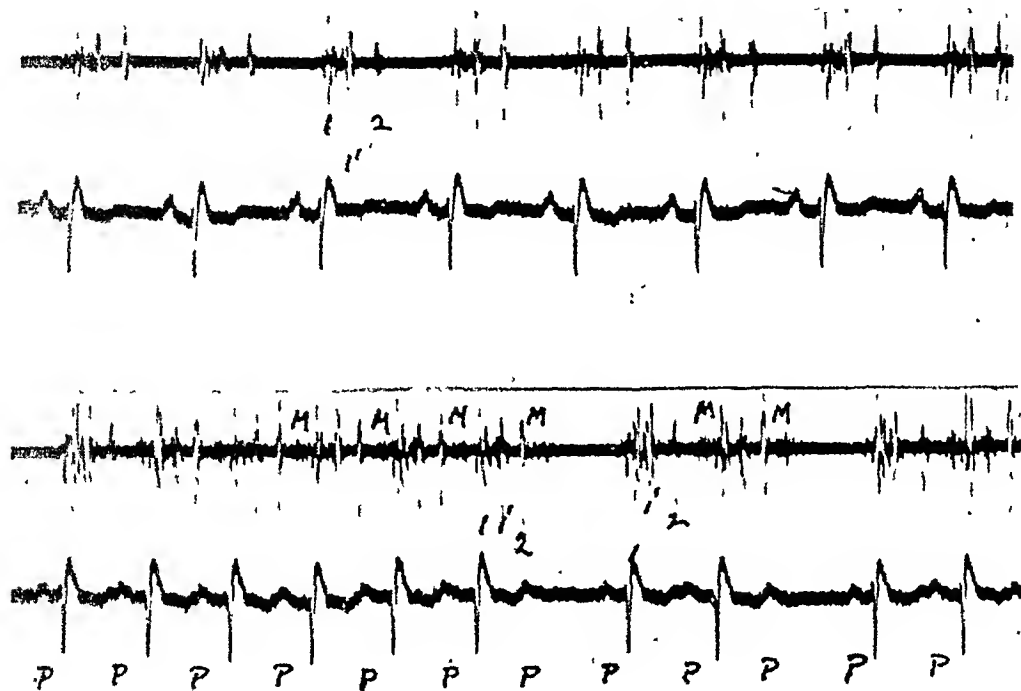


FIG. 13.—Case 9. Heart sounds at the apex and electrocardiogram. Above, sinus rhythm, P-R interval, 0.18 second. The first heart sound is widely split, 1, 1', with an unlabeled murmur between the two components and a few presystolic vibrations (not thought to constitute a murmur) before the first component. Below, auricular tachycardia with Wenckebach periods. Vibrations of an auricular murmur, M, are visible with lengthening P-R intervals and especially in cycles with complete block.

OBSERVATIONS

A blowing murmur restricted to the apex was clearly heard during ventricular diastole in each of the cases described. Records of the heart sounds in all nine cases showed the vibrations of a murmur, as distinguished from the usual abrupt auricular sounds which occur with heart block, although the latter were occasionally found also. The murmur was louder with the patient in the left lateral recumbent or supine position but could be heard in the upright position except when auricular fibrillation was present. With complete heart block its temporal position varied from cycle to cycle, depending upon the time of auricular activity.

It could then usually be heard twice in each cycle and was always louder when it appeared fairly early in diastole. There was no opening snap of mitral stenosis in any of the patients, and the murmur was never constantly related to the second heart sound except as noted later in the paper.

The following measurements were made on simultaneous records of the heart sounds and an electrocardiographic lead, avoiding parallax; in some cases cardiovascular pulsations were also recorded. It is recognized that these data are not as accurate as could be desired because of such difficulties as locating the earliest vibrations of the murmur. Nevertheless, some of the findings seem significant.

Interval from P Wave to Murmur.—The interval between the onset of the P wave of the electrocardiogram and the onset of the murmur averaged 0.15 to 0.16, 0.16, 0.23, 0.18, 0.14 to 0.16, 0.17, 0.16, and 0.18 second in Cases 1 through 8, respectively.

Interval From Second Heart Sound to Murmur.—Except under special conditions, there was no murmur related by a definite time interval to the second heart sound. In Case 1 a murmur was often recorded with onset about 0.12 second after the second sound whenever a P wave began just before that sound (Fig. 1). The amplitude of these vibrations was less than when the murmur appeared later in diastole. In Case 4, the second heart sound often preceded a murmur by 0.06 to 0.08 second whenever the P wave fell comparatively late in ventricular systole (Fig. 8).

With auricular fibrillation in Cases 1 and 2, a faint apical murmur was found in early diastole (Figs. 2 and 5). It started about 0.19 second after the second heart sound in Case 1, 0.12 second or less in Case 2.

Auricular Sounds.—In some of the patients phonocardiograms at times revealed abrupt auricular sounds, as distinguished from murmurs.

In Case 1, vibrations incorporated within the auricular murmur resembled those of a sound when the murmur began, roughly, 0.3 to 0.6 second after the second heart sound. These vibrations occurred about 0.21 second after the start of the P wave.

In Case 4, the murmur was only heard very early in ventricular diastole. Phonocardiograms (Fig. 7) show that its vibrations became small rather suddenly, in different cycles, whenever the P wave began later than about 0.5 second after the last second heart sound. With P waves later than that, there were a few small, slow vibrations starting 0.20 second after the onset of the P wave. These did not differ appreciably whether their associated P wave began 0.6 or 1.3 second after the last second heart sound. They were sometimes identified on auscultation as faint, double auricular sounds but were usually inaudible. In this patient, in whom the murmur of ventricular systole was short and faint at the apex, a loud clicking auricular sound was occasionally heard and recorded before the second heart sound. Late in ventricular systole such sounds started 0.10 second after the P wave, while earlier in systole the interval was about 0.14 second. The recorded appearance of the sound varied (Fig. 8) and occasionally even resembled that of a murmur.

In Case 5, with 2:1 block, auricular sounds were associated with both blocked and conducted (P-R interval, 0.45 second) P waves. With the latter, double auricular sounds (faintly audible but not separated on auscultation) were recorded. The first component occurred 0.14 second and the second component 0.28 second after the onset of the P wave. The blocked P wave, which started 0.06 second after the second heart sound, was followed 0.16 second after its onset by a loud third heart sound which was noted clinically and initiated the auricular murmur. On the other hand, records occasionally showed vibrations which looked like a murmur with the conducted cycle. Finally, the usual murmur following the third sound was sometimes absent. In this event there was usually a fourth sound, 0.16 second after the third and associated with a downward deflection of the apex beat curve (Fig. 9). In this patient, records made during complete block showed only a murmur, starting 0.14 to 0.16 second after the P wave.

In Case 7, especially with the patient in the left lateral recumbent position, the murmur was sometimes initiated or replaced by a recorded vibration which had the appearance of a sound (Fig. 11). A mid-systolic click was also noted.

Apex Beat.—In Case 5, a sharp upward deflection of the apex beat curve accompanied the third sound, which followed the onset of the blocked P wave by 0.16 second and which was at once followed by the auricular murmur (see also preceding section). In the same patient, the second component of the auricular sound with conducted P wave was associated in the apex beat with a sharp downward deflection 0.28 second after the onset of the P wave, followed at once by a slow rise (Fig. 9).

A similar slow, small rise in the apex beat curve began 0.16 to 0.24 second after the onset of the P wave in Case 2 and 0.16 second in Cases 3 and 8. The significance of this rise is not clear, but it is not thought to represent auricular systole.

In Case 4 (Fig. 8) a larger upward movement of the recorded apex beat began 0.14 second and reached its peak 0.22 second after the onset of the P wave. It did not occur with P waves during ventricular systole and its appearance and timing did not vary with the location in ventricular diastole, a finding which may be related to the following observation.

Jugular a Wave.—The behavior of the jugular *a* wave was especially noteworthy in Case 4. When the *a* wave occurred late in ventricular diastole without an audible murmur, its amplitude was no greater than that of an *a* wave associated with a murmur early in diastole. The same records show markedly increased amplitude of *a* waves during ventricular systole, as expected (Fig. 7). Judging by this observation, ventricular filling even for 1.3 seconds after the last second heart sound (and further aided by two intervening auricular systoles) does not impede outflow from an auricular contraction occurring late in ventricular diastole.

In Cases 2 and 4, the murmur began at or after the peak of the *a* wave, a point which was also associated with the first component of the double auricular sound in Case 5.

The jugular *a* wave began 0.08, 0.10, 0.10, and 0.09 second after the onset of the P wave in Cases 2, 4, 5, and 6, respectively. Since these findings are in the normal range, they indicate no delay in right-sided auricular systole.

DISCUSSION

Mitral Stenosis.—An apical murmur related to auricular activity is at once suggestive of mitral stenosis, but that lesion did not appear to be present. Calcification of the mitral annulus fibrosus, such as found in Cases 1 through 4, might be expected to obstruct flow through that orifice but actually does so only rarely; in five other patients with calcification but with P-R intervals of 0.14 to 0.18 second this murmur could not be heard or recorded.¹

No patient had the other physical signs of mitral stenosis; namely, loud or split pulmonic second sound, loud first heart sound (except when accentuated in cycles with short P-R intervals), opening snap, or early diastolic murmur constantly related to the second sound (in the absence of auricular fibrillation). Right axis deviation was never present, nor was the P wave abnormally large. The left auricle was not often prominent, except with general cardiac enlargement or auricular fibrillation. Although the auricular murmur was enhanced in the left lateral recumbent position, it was usually blowing in quality, quite unlike the rumble of rheumatic mitral stenosis; in Case 2 it was rather rough, and in Case 4 became rumbling after several years.

Aortic regurgitation was not present, so the Austin Flint murmur need not be considered. An auriculo-systolic murmur which has been heard at the tricuspid area during convalescence from myocardial infarction² is likewise unrelated to the present discussion.

A murmur suggestive of mitral stenosis has been found in patients without that lesion but with anemia^{3,4} or congestive heart failure^{5,6} and is usually attributed to stenosis relative to dilated cardiac chambers. While congestive failure was sometimes present, it was never more than mild when the foregoing observations were made in these ambulatory patients, of whom none was anemic. Heart block itself produces cardiac dilatation but has never been thought to cause a murmur. Stenosis of the mitral orifice relative to such distention should give a murmur louder in later diastole, whereas the opposite was true.

One of the main reasons for rejecting mitral stenosis, actual or relative, as the cause of the murmur is the latter's delayed onset after the P wave. Probably because of the difficulties in locating accurately the onset of a murmur in records of the heart sounds, there are but few data to indicate the temporal relationships of the presystolic murmur in rheumatic mitral stenosis. Calculations based on the observations of Lewis⁷ and Bramwell⁸ suggest that such a murmur starts 0.03 to 0.15 second after the beginning of the P wave, with which a few records in this laboratory agree. In the present patients the murmur began 0.14 to 0.23 second after the P wave. Their jugular *a* waves revealed no delay in the onset of right auricular contraction, and there is no reason to believe that systole of the left auricle did not coincide with that of the right. Furthermore, it was

possible to find cycles with normal P-R intervals in the patients with complete heart block. At such times vibrations of a murmur were not visible in the phonocardiograms (Figs. 1 and 6).

Temporarily ignoring its presence early in diastole with auricular fibrillation, the murmur appears to be an event which *follows* auricular contraction. The evidence given seems to indicate that it is neither caused by obstruction to flow nor coincident with auricular systole.

Mitral Insufficiency.—It is conceivable that the apical murmur which follows after auricular systole during ventricular diastole is the result of regurgitation of blood back into the auricle, with mitral insufficiency.

If this were the case, a murmur might also be expected to occur at the close of the period of early diastolic rapid filling. This did occur faintly in Cases 1 and 2 during auricular fibrillation, but only then. Regurgitation perhaps should also increase, presumably with a louder murmur, when the ventricles are more full late in diastole. Observations showed the opposite.

Mitral insufficiency as a cause of the murmur would be supported by its demonstration during ventricular systole. With the slow rate of heart block and with arterial hypertension, circulatory conditions were optimal for regurgitation of blood if mitral insufficiency were actually present.⁹ A systolic murmur was frequently heard at the apex, and in a general way its intensity was paralleled by that of the auricular diastolic murmur. However, it was usually fainter at the apex than along the left sternal border, was once confined to the interval between the widely split components of the first heart sound, and was not conspicuous in every case. It might have been produced by aortic dilatation with arteriosclerosis.

It is generally held, though perhaps incorrectly, that mitral regurgitation may be present without radiologic evidence of left auricular dilatation or abnormal pulsation of that chamber in roentgenkymograms. At any rate, the left auricle was not prominent in any of the patients during the period in which most of the observations were made. It did, however, enlarge somewhat later on in Cases 2, 9, and perhaps 4. This might have been the result of auricular fibrillation and progressive congestive failure. Study of the roentgenkymograms in Cases 1, 2, 4, 5, and 6 showed none of the findings thought to be typical of mitral regurgitation.¹⁰

In brief, regurgitation through the mitral leaflets at the close of auricular systole may be a simple explanation for the murmur, but there is little evidence to substantiate its occurrence. The frequent association of the murmur with auricular sounds and its occasional replacement by them are adequate reasons for consideration of other possible mechanisms.

Relation to Heart Block.—The murmur occurred only in patients with heart block. Auricular activity during that arrhythmia ordinarily results in abrupt sounds, not murmurs. At times, phonocardiograms of this event have revealed prolonged vibrations¹¹ which do not appear to have been clinically interpreted as murmurs.

Wolferth and Margolies¹² and Stead and Kunkel¹³ reported two cases of heart block, each with an audible murmur similar to that now being discussed. The causes of block were not altogether clear. There were no other signs of mitral stenosis, and the patients were aged 49 and 57 years. The murmur started 0.14 to 0.16 second after the onset of the P wave. Apparently the murmur was not present in Case 1 of Wolferth and Margolies' series during periods of sinus rhythm with normal P-R intervals. A presystolic murmur was heard and recorded in the case of Stead and Kunkel with the P-R interval as short as 0.20 second (during 2:1 block) and was noted during sinus rhythm with which the P-R interval was never found to be less than 0.22 second.¹⁴ These two cases and the nine reported here seem to be the only recorded instances of audible auricular murmurs in heart block (without obvious mitral stenosis). Such a murmur will surely be found more often in elderly patients with defective auriculoventricular conduction, once the possibility of its occurrence is appreciated.

Limitation of the murmur to patients with heart block must be the result simply of delayed ventricular contraction, permitting an adequate interval of time to elapse after the conclusion of auricular systole; the conditions productive of the sounds or murmurs which may be heard in this interval would otherwise be prevented.

Heart Sounds During Ventricular Filling.—Since the murmur began 0.14 to 0.23 second after the start of the P wave, or about 0.12 to 0.19 second after the second sound in the presence of auricular fibrillation, it becomes pertinent to inquire into what is known of cardiodynamics and sounds during those periods.

Early in diastole, ventricular filling commences abruptly at the time indicated by the position of the opening snap of mitral stenosis, 0.07 to 0.13 second after the second heart sound.¹⁵ This phase of rapid filling comes to an end 0.12 to 0.20 second after the second sound. Here a normal third heart sound or an early diastolic gallop may be present¹⁵ and this is the range of time in which the murmur began in Cases 1 and 2 in the presence of auricular fibrillation.

In both laboratory animals and man,¹⁶ auricular systole appears to begin about 0.03 to 0.04 second, and the jugular *a* wave about 0.08 to 0.10 second, after the start of the P wave. In at least four of the present patients jugular *a* waves indicated no delay in the onset of mechanical systole of the right auricle. The duration of increased intra-auricular pressure may be 0.13 to 0.15 second.^{17,18} Therefore, the phase in which ventricular filling is accelerated by auricular systole is at an end some 0.16 to 0.19 second from the start of the P wave. This, roughly, is in the time range of the onset of the murmur now under discussion. It is also near the time at which another sound may be recorded; while a presystolic gallop is often found 0.08 to 0.14 second after the beginning of the P wave, this interval lengthens in ambulatory patients with milder congestive failure to 0.12 to 0.17 second.¹⁹

Some of the auricular sounds found in heart block follow the P wave by an even greater interval. Omitting a preliminary sound recorded only from the auricular wall or through the esophagus, two groups of workers^{11,20} place the first

component of audible auricular sounds at 0.06 to 0.08 or 0.12 second and the second component at 0.17 to 0.24 or 0.20 to 0.24 second from the start of the P wave. Our findings are in better agreement with Wolferth and Margolies,¹⁵ who give intervals of 0.08 to 0.14 and 0.24 to 0.30 second, respectively, for the two components. We also agree with the latter observers that it is only the first component which is recorded during ventricular systole.

At least part of the variations and discrepancies in the foregoing data may result from differences in age, degree of heart failure, presence of valvular or other lesions, etc., in the patients studied; it might be more helpful if future workers on heart sounds considered some of these factors. Clarification of the present uncertainties as to the causes of diastolic sounds would obviously be greatly desirable.

Based in part on Dean's²¹ experiment, Lewis and Dock^{22,30} suggested that the third heart sound and gallop sounds may occur at the end of rapid-filling phases if the auriculoventricular valve leaflets are then closed or drawn taut. Not all workers agree with this view.¹⁵ Dean,²¹ using the excised heart of the cat, found that the mitral cusps swing up and are momentarily approximated at about 0.15 second after the start of mechanical auricular systole. The cusps separate again 0.12 second later. These times come 0.18 and 0.30 second after the onset of the P wave, and the first is compatible with the start of the murmur; for comparison with Dean's time of valvular separation, the final vibrations of the murmur occurred about 0.31 to 0.37 second after the onset of the P wave in Cases 1 through 6. There is, of course, an obvious risk in comparing events in excised cat hearts and abnormal human hearts.

The data presented in this section are consistent with the view that the murmur in these elderly patients starts near the end of phases of accelerated ventricular filling, at times when short sounds may be heard in other subjects. Such sounds, in fact, occurred in the present patients occasionally, either replacing the murmur or associated with it. The temporal relationships of the murmur are similar to those of a period during which experimental studies have demonstrated the approximation of mitral leaflets following auricular systole. Approximation was not found after the early diastolic phase of rapid filling,²¹ nor did the murmur occur then except twice; on both occasions auricular fibrillation was present and the murmur was much fainter.

It seems very likely that the murmur is produced by some mechanism which does not interfere with the movements of the valve leaflets during periods of rapid flow but which modifies their presumably more delicate aftermovements.

Aging of the Valve Leaflets.—This sort of mechanism might have an anatomic explanation in the increased thickness and rigidity of valve leaflets known to occur with advancing years, especially on the left side of the heart.²³⁻²⁵ There seems to be no direct information regarding the effect of aging on the mobility of leaflets, but some indirect data may have a bearing.

Wolferth and Margolies¹² found, in two young patients with heart block, two zones of intensification of the first heart sound; the first was with P-R in-

tervals of less than 0.14 to 0.20 second, the second with P-R intervals greater than 0.32 second. In three older patients the second zone was not present. These findings have been confirmed by unpublished observations in this laboratory. Expressing the results differently, the first heart sound is relatively faint in children when the P-R interval is between 0.14 to 0.20 and 0.32 second, the time of the murmur in our patients and that of approximated mitral leaflets in Dean's²¹ experiment. It is faint in elderly patients at all times after P-R intervals of 0.14 to 0.20 second.

The explanation of the variable intensity of the first heart sound in block is not entirely clear, but the hypothesis that accentuation takes place whenever "systole occurs at an instant when inflow from the auricle is pushing the valves toward the apex and separating the leaflets as much as possible"²² is attractive and appeals to others.¹³ The corollary is a faint first heart sound whenever the leaflets are approximated at the onset of ventricular systole. According to this view, the mitral leaflets of children swing apart again some 0.32 second after the P wave, while those of older subjects do not.

The forces concerned with the play of the cardiac valves during ventricular diastole are not definitely known²⁶ but may involve eddy currents or "the lateral inrush into the wake of the breaking jet just beyond the ostium."²⁷ An inrolling type of motion of pliable young leaflets with the force of lateral inrush is thought to close the valve without regurgitation; rigid old leaflets, swinging like a door on hinges, may permit regurgitation.²⁷ Furthermore, the leaflets of the elderly are said to be "less nicely approximated"²³ than in youth, again suggesting regurgitation as the cause of the murmur.

On the other hand, these forces may be sufficient to narrow the mitral orifice while blood is flowing through in a forward direction,^{18,26} apparently even with thin normal leaflets. If this is so, it is conceivable that the murmur is produced by the more prolonged apposition of thick, rigid cusps under similar conditions, perhaps with vibration of the leaflets.

Since valvular aging appears to begin in the second or third decades, this may be at least a partial explanation for the decreasing frequency of the normal third heart sound with age. Leaflets becoming less pliable might fail at normal pressures to behave in the manner thought to produce the third sound²² but could again respond to the increased intra-auricular pressure of heart failure with a gallop sound.

The Murmur in Relation to Phase of Ventricular Diastole.—In general, records of the heart sounds revealed that the greatest amplitude of the murmur's vibrations was found when the murmur began near the end of the early diastolic rapid-filling phase (Figs. 1, 3, 6, 7, 8, and 10). The vibrations were usually smaller after this period, except for a few of large amplitude, as if a sound were bracketed by the murmur. They were certainly smaller before this period. This fact may be less significant because the associated P wave often started in or near the end of ventricular systole.

Other observers^{8, 12, 17} have also noted the diminishing intensity of auricular murmurs in heart block as auricular activity comes later in ventricular diastole. Their logical explanation is that during diastole the filling ventricle becomes less able to receive blood with later or successive auricular contractions. This is so obvious that it came as a surprise to find both old²⁸ and new¹⁸ experiments which suggest that this need not be so.

In Case 4 the behavior of the jugular *a* wave failed to reveal right ventricular inability to receive blood late in diastole. Its amplitude and duration were no greater when it occurred more than 0.5 second after the second sound, without appreciable murmur, than when it occurred less than 0.5 second after the second sound and with a murmur (Fig. 7). With the closed valve of ventricular systole, the *a* wave was tall, as expected. In fact, the tracing seems to show broader and less peaked *a* waves *early* in diastole, especially with the earliest and greatest murmurs. If this is significant at all, it is in the direction of supporting the concept of greater resistance to auricular systolic ejection when this comes with the early rapid-filling phase.¹⁸

In other patients the murmur occurred at any time in diastole, starting as late as 0.8, 0.9, and 1.1 seconds following the last second heart sound in Cases 1, 3, and 5, even though the auricles had contracted once before in those cycles. Closer inspection of Fig. 14 for Case 1 of Wolferth and Margolies' series¹² lends further support to the conception that the murmur's amplitude is not so much decreased in late diastole as it is increased when approaching the zone of the third heart sound. The latter was pointed out in their legend.

When the P-R interval of the final P wave in a ventricular diastole was 0.20 second or less, no vibrations of a murmur were recognizable. With P-R intervals just a few hundredths of a second longer, vibrations were readily apparent (Figs. 1 and 6). Such a short difference of time cannot well explain the absence of the murmur by further ventricular filling in that interval but must be taken as confirmation of a relatively late onset of the murmur after the P wave. This is analagous to the absence of a murmur in elderly patients with normal conduction times.

Incidentally, the first heart sound was accentuated in Cases 1, 3, 4, and 5 with short P-R intervals, but not when the P-R interval was long enough, 0.20 second or more, to permit recognition of a murmur's vibrations. This probably means the mitral leaflets were no longer widely separated by auricular systole when the murmur was produced, in further agreement with its delayed onset.

The early, rapid-filling phase failed to provoke any but a faint murmur which occurred twice and only with auricular fibrillation. Even auricular systole was not always followed by the murmur, especially after a long diastole. Apparently the two events are more powerful when in conjunction, in which connection it is interesting that Cossio²⁹ found a third sound with heart block when the P wave fell immediately after the T wave of the preceding cycle in patients who otherwise had neither auricular sounds nor third heart sounds.

As an alternative to mitral regurgitation, the following hypothesis is proposed. After auricular systole, normal mitral leaflets are floated nearly together. In

the aged, they remain longer and more fixed in that position because of their increased rigidity. The murmur occurs then with continuing forward flow through the relatively narrow orifice. It is loudest in the part of early diastole which follows the phase of rapid filling because the valvular play after this event reinforces the valvular play after auricular systole and because the blood flow is still great. When the murmur disappears or is replaced by the usual short auricular sounds in late diastole, it is because the flow has become slow. This is more the result of moving away from the early phase of rapid filling than of ventricular inability to receive blood. The lesion is not adequate to hamper flow during the rapid ejection phases themselves.

SUMMARY AND CONCLUSIONS

Observations are reported on a blowing apical murmur related to auricular activity in nine elderly patients with heart block. At times the murmur was associated with, or replaced by, short auricular sounds.

There was no convincing evidence of rheumatic mitral stenosis. Calcification of the mitral annulus fibrosus was demonstrated in four cases. Other patients with this lesion but without conduction defects do not have such a murmur.

The onset of the murmur seemed to occur just after the end of auricular systole. In the presence of auricular fibrillation, it began near the end of the rapid-filling phase of early diastole. These are the times at which gallop sounds may be present in other patients.

In the absence of auricular fibrillation, there was no murmur in relation to the second heart sound unless auricular activity happened to take place at that time.

The murmur was loudest when auricular activity more or less coincided with the end of the early rapid-filling phase. Both earlier and later in diastole, the murmur was fainter.

An explanation other than inability of the filled ventricle to receive blood late in diastole is offered to account for the diminished intensity of the murmur at that period.

Mechanisms which might be responsible for the production of the murmur are discussed in relation to current conceptions of cardiodynamics and heart sounds during ventricular diastole.

Reasons are given for believing that the murmur may be caused by modifications of the movements of the mitral valve leaflets at the end of periods of accelerated ventricular filling, especially after auricular systole.

The lesion responsible for such a mechanism may be the result of aging of the leaflets, without interference to flow during rapid ejection phases.

It is further suggested that aging of the leaflets could account for the disappearance of the normal third heart sound and its return as a gallop during heart failure.

This is another murmur which may be heard at the cardiac apex during diastole in the absence of mitral stenosis.

REFERENCES

1. Rytand, D. A., and Lipsitch, L. S.: Clinical Aspects of Calcification of the Mitral Annulus Fibrosus, *Arch. Int. Med.* In press.
2. Wolferth, C. C., Wood, F. C., and Margolies, A.: An Auriculosystolic Murmur in the "Tricuspid Area" During Convalescence From Acute Coronary Occlusion, *Am. J. Med. Sc.* 186: 496, 1933.
3. Goldstein, B., and Boas, E. P.: Functional Diastolic Murmurs and Cardiac Enlargement in Severe Anemia, *Arch. Int. Med.* 39: 226, 1927.
4. Winsor, T., and Burch, G. E.: The Electrocardiogram and Cardiac State in Active Sickle-Cell Anemia, *AM. HEART J.* 29: 685, 1945.
5. Weinstein, W., and Lev, M.: Apical Diastolic Murmurs Without Mitral Stenosis, *AM. HEART J.* 23: 809, 1942.
6. Robinow, M., and Harper, H. T., Jr.: Functional Mitral Stenosis, *Ann. Int. Med.* 17: 823, 1942.
7. Lewis, T.: The Time Relations of Heart Sounds and Murmurs, With Special Reference to the Acoustic Signs in Mitral Stenosis, *Heart* 4: 241, 1912.
8. Bramwell, C.: Sounds and Murmurs Produced by Auricular Systole, *Quart. J. Med.* 4: 139, 1935.
9. Wiggers, C. J., and Feil, H.: The Cardiodynamics of Mitral Insufficiency, *Heart* 9: 149, 1922.
10. Hirsch, I. S., and Gubner, R.: Application of Roentgenkymography to the Study of Normal and Abnormal Cardiac Physiology, *AM. HEART J.* 12: 413, 1936.
11. Orías, O., and Braun-Menéndez, E.: *The Heart-Sounds in Normal and Pathological Conditions*, London, 1939, Oxford University Press.
12. Wolferth, C. C., and Margolies, A.: The Influence of Auricular Contraction on the First Heart Sound and the Radial Pulse, *Arch. Int. Med.* 46: 1048, 1930.
13. Stead, E. A., Jr., and Kunkel, P.: Factors Influencing the Auricular Murmur and the Intensity of the First Heart Sound, *AM. HEART J.* 18: 261, 1939.
14. Stead, E. A., Jr.: Personal communication.
15. Wolferth, C. C., and Margolies, A.: Heart Sounds. In Stroud, W. D. (editor): *The Diagnosis and Treatment of Cardiovascular Disease*, ed. 3, Philadelphia, 1945, F. A. Davis Co., vol. 1, pp. 545-592.
16. Taquini, A. C.: *Exploracion del Corazon Por Via Esofagica*, Buenos Aires, 1936, El Ateneo, p. 32.
17. Wiggers, C. J.: The Physiology of the Mammalian Auricle. I. The Auricular Myogram and Auricular Systole, *Am. J. Physiol.* 40: 218, 1916.
18. Jochim, K.: The Contribution of the Auricles to Ventricular Filling in Complete Heart Block, *Am. J. Physiol.* 122: 639, 1938.
19. Lewis, J. K.: Nature and Significance of Heart Sounds and of Apex Impulses in Bundle Branch Block, *Arch. Int. Med.* 53: 741, 1934.
20. Cossio, P., Berconsky, I., and Trimani, A.: Genesis de los Ruidos Auriculares Diastolicos en el Bloqueo Auriculoventricular Completo. *Rev. argent. de cardiol.* 9: 238, 1942.
21. Dean, A. L., Jr.: The Movements of the Mitral Cusps in Relation to the Cardiac Cycle, *Am. J. Physiol.* 40: 206, 1916.
22. Lewis, J. K., and Dock, W.: The Origin of Heart Sounds and Their Variations in Myocardial Disease, *J. A. M. A.* 110: 271, 1938.
23. Colm, A. E.: Cardiovascular System and Blood. In Cowdry, E. V. (editor): *Problems of Ageing*, ed. 2, Baltimore, 1942, The Williams & Wilkins Co., pp. 111-138.
24. Wearn, J. T., and Mortiz, A. R.: The Incidence and Significance of Blood Vessels in Normal and Abnormal Valves, *AM. HEART J.* 13: 7, 1937.
25. Gross, L., and Kugel, M. A.: Topographic Anatomy and Histology of the Valves in the Human Heart, *Am. J. Path.* 7: 445, 1931.
26. Wiggers, C. J.: *Physiology in Health and Disease*, ed. 4, Philadelphia, 1944, Lea and Febiger, p. 611.
27. Henderson, Y., and Johnson, F. E.: Two Modes of Closure of the Heart Valves, *Heart* 4: 69, 1912.
28. Gesell, R. A.: Auricular Systole and Its Relation to Ventricular Output, *Am. J. Physiol.* 29: 32, 1911; Cardiodynamics in Heart Block as Affected by Auricular Systole, Auricular Fibrillation and Stimulation of the Vagus Nerve, *Am. J. Physiol.* 40: 267, 1916.
29. Cossio, P.: *Temas de Fonocardiografía*, Buenos Aires, El Ateneo, 1936, p. 87.
30. Dock, W.: Further Evidence for the Purely Valvular Origin of the First and Third Heart Sounds, *AM. HEART J.* 30: 332, 1945.

HYPERTROPHY OF THE HEART OF UNKNOWN ETIOLOGY IN YOUNG ADULTS: REPORT OF FOUR CASES WITH AUTOPSIES

COMMANDER ROBERT F. NORRIS, M.C., AND LIEUTENANT COMMANDER HARRY
H. POTE, M.C., UNITED STATES NAVAL RESERVE

IN ONE year at the Philadelphia Naval Hospital, four men between the ages of 21 and 30 years, with histories of progressive congestive failure, died of unexplained hypertrophy and dilatation of the heart. Neither clinically nor at autopsy was the etiology of the hypertrophy determined. All of them had been under repeated medical observation for at least two years and at no time, even before the onset of cardiac symptoms, was there any evidence of hypertension or of other factors which commonly result in hypertrophy of the heart. At autopsy, there was no valvular disease and the large and small coronary arteries were considered normal for this age. Hypertrophy of individual muscle fibers was the most conspicuous microscopic abnormality. There was evidence of focal degeneration of the myocardium, but the lesions were not so extensive as to constitute a diffuse myocarditis.

Although cases of unexplained sudden death presumably of cardiac origin during this period of life are occasionally seen at autopsy, particularly by coroner's physicians, hypertrophy of the heart in the absence of anatomic defects is usually not pronounced. In the present cases, however, death, although at first unexpected, was not sudden except in one patient (Case 2), occurred only after progressive congestive failure, and was associated with distinct hypertrophy of the heart. In older patients, clinically unexplained congestive failure and hypertrophy of the heart are usually ascribed to a previously unrecognized hypertension or to arteriosclerosis of the smaller coronary arteries and arterioles. In none of the cases to be described was there any evidence of either of these factors.

In 1933, Levy and Rousselot¹ reported three cases of similar age which resemble ours, but found only two others^{2,3} in the literature. In 1937 Levy and Von Glahn⁴ reported eight cases from 29 to 66 years of age. Since that time, we have found no further reports. In view of the rarity of unexplained hypertrophy of the heart in the third decade, therefore, a report of four such cases is justified.

Now at the William Pepper Laboratory of Clinical Medicine, University of Pennsylvania, Philadelphia, Pa.

The opinions or assertions contained herein are the private ones of the writers and are not to be construed as official or reflecting the views of the Navy Department or the naval service at large.

Received for publication April 10, 1946.

REPORT OF CASES

Case 1

Previous History.—J. U., a white man, aged 28 years, was admitted to the Philadelphia Naval Hospital on Aug. 9, 1944, complaining of shortness of breath and swelling of ankles of about three weeks' duration. The family and past medical histories were irrelevant. He enlisted in the United States Coast Guard on April 19, 1940, and had no overseas duty. He was apparently discharged on Nov. 17, 1942. At this time an appendectomy with drainage was performed for gangrenous appendicitis. He had no further abdominal complications and the incision healed satisfactorily. On the fourth postoperative day, he had fever and cough and was thought to have pneumonia, but this was not confirmed since no x-ray examination of the chest was made. These symptoms subsided in a few days, however, without the administration of sulfonamides. An x-ray film of the chest on the twelfth postoperative day showed no evidence of pneumonia but revealed the heart to be symmetrically enlarged. Without further study, he was discharged to active duty on Dec. 12, 1942, the eighteenth postoperative day. On Jan. 4, 1943, because of exertional substernal pain and palpitation of three days' duration, he was readmitted to a hospital. Except for an enlarged heart, no significant findings were reported on physical examination. He was discharged from the service because of heart disease on Feb. 12, 1943. The highest blood pressure was 120/90. He was always afebrile.

Following discharge he was asymptomatic and was able to work as a packer for nearly eighteen months. During this period he was examined frequently at a Veterans' Administration facility, and no further abnormalities were discovered. On July 18, 1944, however, he noticed shortness of breath and on the advice of a family physician he stopped work. The dyspnea persisted, even while at rest, and on August 9, he coughed up blood-tinged sputum and noticed that his ankles were swollen. He was admitted for the first time to this hospital on the same day.

On admission he was cyanotic and orthopneic. The legs were markedly edematous. The heart was greatly enlarged, the rhythm was regular, and the heart rate was 124 per minute. There were no murmurs. Blood pressure was 100 systolic, but the diastolic was not determined. Numerous râles were heard over the lungs and the liver was enlarged three fingerbreadths below the right costal margin. He grew progressively worse and died on Sept. 11, 1944, thirty-three days after admission.

Laboratory Data.—During hospitalization for appendectomy, no electrocardiogram was made. On the second admission, an electrocardiogram was reported as normal. On final admission, an electrocardiogram before digitalis was given showed left-axis deviation, QRS interval of 0.16 second, indicating bundle-branch block, elevation of RS-T segment in Leads II and III and depression in Lead CF₄, and inversion of T waves in Lead I (Fig. 1). At the time of the appendectomy, there was a transient leucocytosis, and shortly before death the white blood count was 33,000, of which 91 per cent were polymorphonuclear neutrophils. A sedimentation rate was not determined at this time but was previously normal. Other laboratory data, including urinalysis, red blood cell count, hemoglobin, blood Kahn, and blood urea nitrogen were within normal limits.

Autopsy (No. 44-182).—

Anatomical Diagnosis: There were hypertrophy and slight focal scarring of myocardium; marked dilatation of all chambers of heart; chronic passive congestion of the lungs and liver; lobular pneumonia; slight atherosclerosis of the aorta; former operative removal of the appendix; and an operative scar in the right lower quadrant of abdomen.

Body: The body and the individual organs grossly and microscopically showed extensive chronic passive congestion, but there were no other relevant lesions except for terminal pneumonia.

*Heart:** The heart weighed 890 grams. The myocardium of both ventricles was hypertrophied but there were no focal lesions. Both auricles and ventricles were greatly dilated. Although the valves were all thin and delicate, the endocardium of the left auricle was opaque and

*Since the hearts of all cases grossly showed only hypertrophy and dilatation, photographs are not included.

slightly but diffusely thickened. The coronary arteries were patent. Only very small atheromatous patches were present in their intima.

Microscopically in numerous sections, including both ventricles, both auricles, and the mitral and aortic valves, there were no areas of inflammation. The muscle fibers of the left ventricle were diffusely hypertrophied and those of the left auricle and ventricle were also increased in thickness. Minute areas of stellate scarring were present in the left ventricle but not elsewhere in the myocardium. The small branches of the coronary arteries were normal.

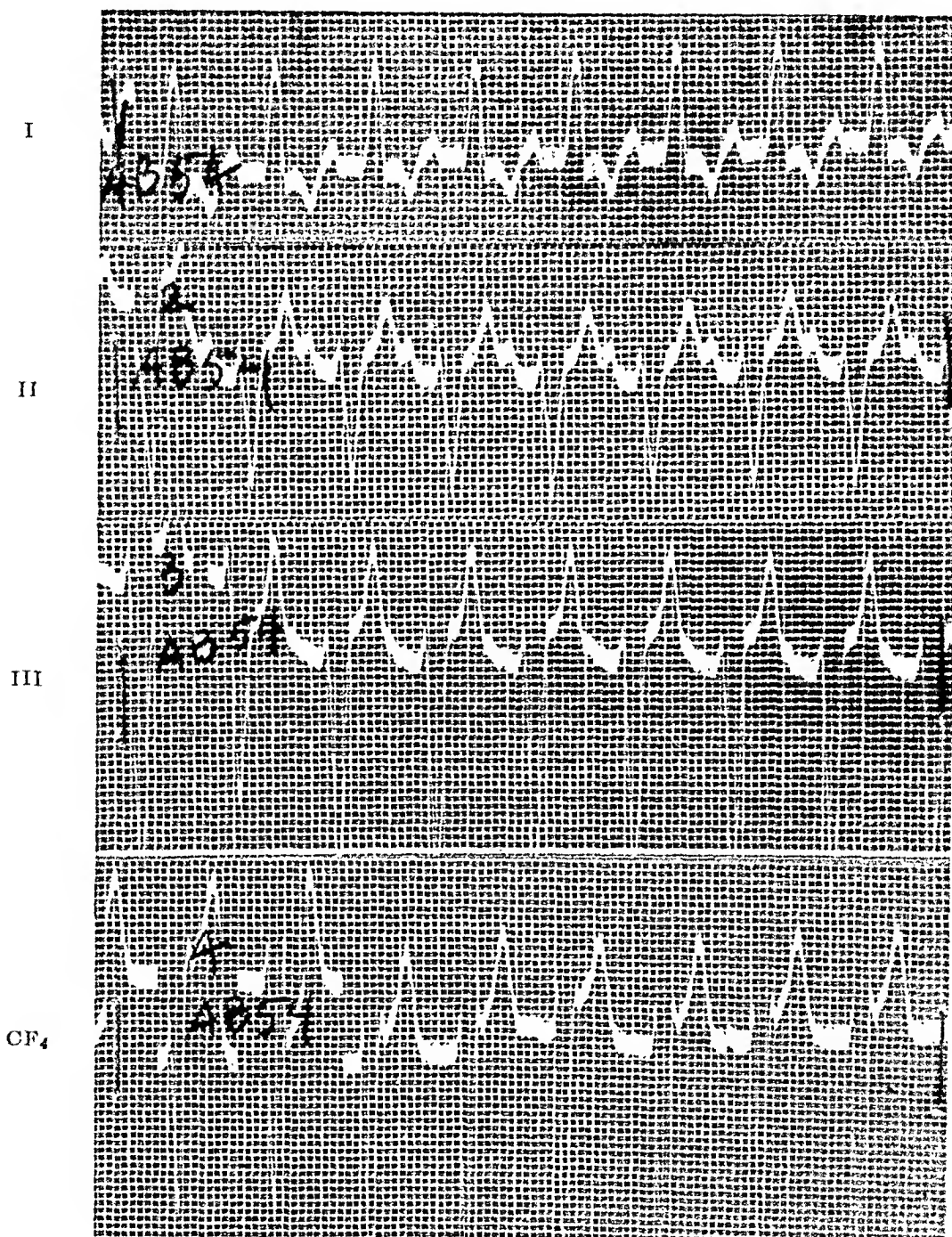


Fig. 1.—Case 1.—There are left-axis deviations; QRS interval of 0.16 second; elevation of RS-T segment in Leads II and III and depression in Lead IV; and inversion of T waves in Lead I; probable bundle-branch block.

CASE 2.—

Clinical History.—E. P. M., a white man, aged 21 years, was admitted to the Philadelphia Naval Hospital on Aug. 22, 1944, complaining of severe pain in the chest of a few hours' duration. The family and past medical histories were irrelevant. He enlisted in the United States Army some time prior to July, 1942. He had no overseas duty. He was apparently well until some time in June, 1943, when he had a "cold" which was followed by cough, weakness, and dyspnea on exertion. The cough subsided but the weakness and dyspnea continued and he began to lose weight. He was first admitted to the sick list because of these symptoms on July 14, 1943. At that time, the only abnormalities, on physical examination, were pallor and small blood clots in the nasopharynx. He was found to have a severe anemia which was considered to be hypochromic and either microcytic or normocytic. Following one transfusion with whole blood and treatment with liver extract, iron, and multiple vitamins, the blood count rapidly returned to normal and he was discharged to duty on Sept. 3, 1943. He was well until about the middle of December of the same year, when the symptoms of weakness and susceptibility to fatigue returned and persisted until the time of his second admission on Jan. 5, 1944. He had lost about fifteen pounds since his discharge and again was pale and anemic. Treatment with whole blood transfusions, liver extract, iron, and multiple vitamins was again effective, but whenever this regimen was discontinued the anemia recurred. At this time an x-ray film of the chest showed a normal cardiothoracic ratio, but the heart appeared to have enlarged when compared with the cardiac silhouette of July, 1943. Since there was also electrocardiographic evidence of myocardial change, he was discharged from the service on April 8, 1944. At this time he had a normal blood count and was asymptomatic. During the periods of hospitalization, the blood pressure was never above 110/85. He was always afebrile.

Following his discharge he had worked regularly and remained well until Aug. 22, 1944, when he was admitted to this hospital because of sudden, severe, persistent precordial pain.

On admission he was cyanotic and orthopneic. The ankles were moderately edematous; the heart was moderately enlarged, the rhythm was regular, the rate was 112, and a soft systolic murmur was localized at the apex. The blood pressure was 110/85. Many râles were heard over both lungs, and the liver was easily palpable. He did not improve and died eight hours after admission.

Laboratory Data.—At the time of the first admission, the red blood cell count was 1,860,000, and the hemoglobin was 34 per cent. The volume index was 0.86 and the hematocrit was 13. There was marked hypochromia and poikilocytosis, but no macrocytes or nucleated red cells were reported. The count was normal on discharge. On the second admission, the red cell count was 2,700,000 with a hemoglobin of 42 per cent. Thereafter it varied somewhat between these figures and normal but was normal on discharge in April. On the day of death the red cell count was 4,410,000, but the hemoglobin was 11.5 grans. Before discharge from the service, repeated electrocardiograms showed a left bundle-branch block, the time of which was 0.16 second. On the day of death an electrocardiogram also showed a QRS complex of 0.16 second and low to inverted T waves in the limb leads (Fig. 2). All other laboratory data during the various periods of hospitalization were within normal limits. These included sedimentation rates, urinalyses, white blood and differential counts, blood sugar and cholesterol, blood Kahns, and basal metabolic rates.

Autopsy (No. 44-196).—

Anatomical Diagnosis: There were history of chronic hypochromic anemia (etiology undetermined); erythroid hyperplasia of bone marrow; hypertrophy and dilation of heart; minute focal necroses and scars in the left ventricle of the heart; chronic passive congestion of the lungs, liver, spleen, and remaining organs; hydropericardium; bloody pleural effusion (bilateral); ascites; peripheral edema; acute phlebitis of the thyroid vein; multiple thrombotic emboli to the lungs; and multiple infarcts of the lungs.

Body: There was moderate pitting edema of the dependent portions of the body. On section, 500 c.c. of blood-tinged fluid were present in the left pleural cavity and 300 c.c. in the right. In the peritoneal cavity there were 300 c.c. of clear straw-colored fluid. There was ex-

tensive chronic passive congestion of all organs. A small vein external to the capsule of the thyroid was occluded by a thrombus which microscopically was necrotic. Several of the arteries in the lower lobes of both lungs were also occluded by thrombi, which showed no evidence of organization microscopically and which were associated with numerous fresh hemorrhagic infarcts of the lungs. In sections of the ribs and vertebral bodies, the erythropoietic elements were increased in number but were otherwise normal.

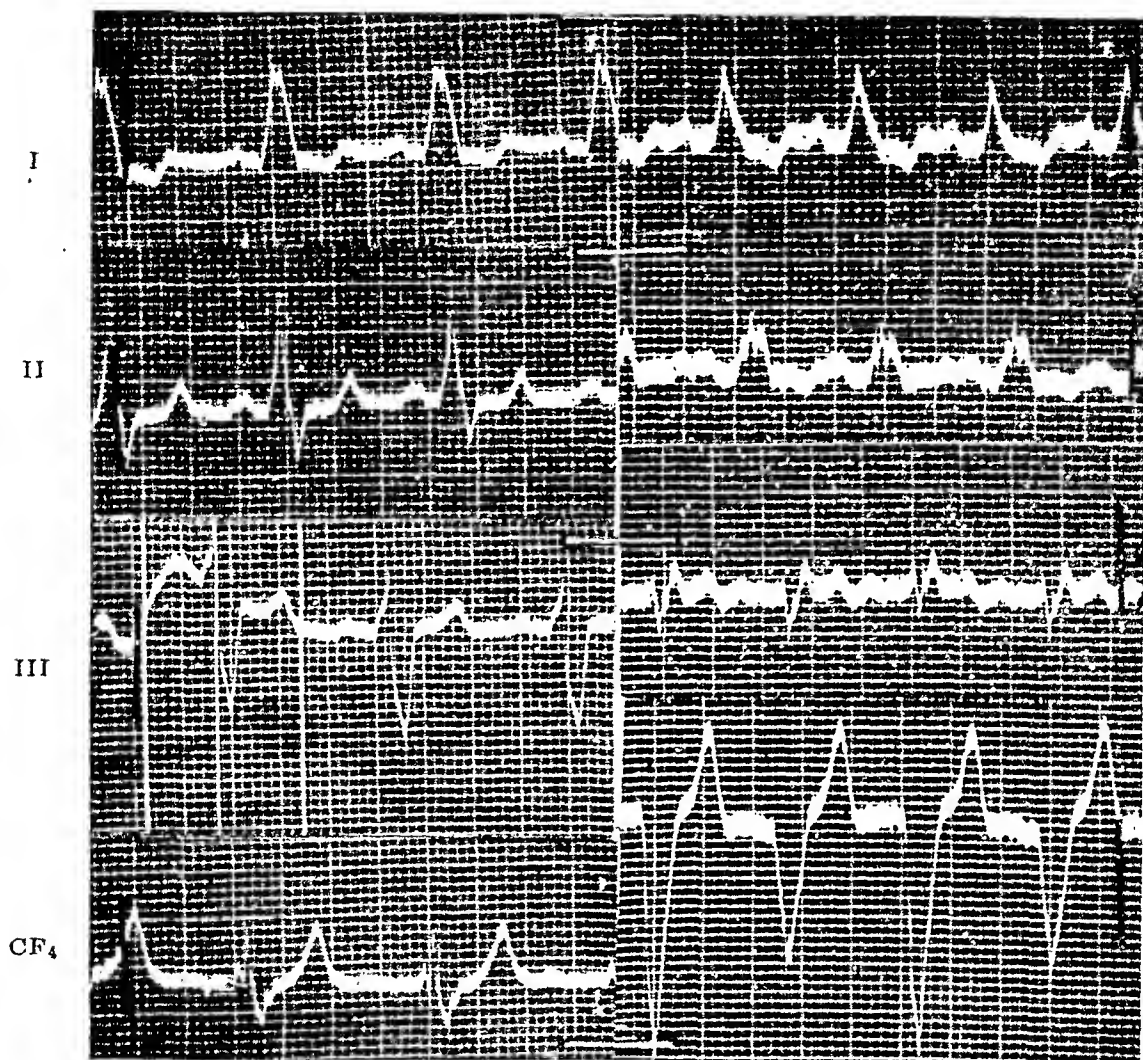


Fig. 2.—Case 2. The QRS interval is 0.16 second in both tracings; on the day of death there are T wave changes.

Heart: The heart weighed 560 grams and the pericardial sac contained 120 c.c. of clear straw-colored fluid. On section of the heart, all of the chambers were dilated and filled with blood. The left ventricle was distinctly hypertrophied but no focal lesions were seen. The valves were all thin and delicate and showed no lesions. The coronary arteries were patent and there were no gross atheromatous plaques in the intima.

Microscopically, numerous sections from both ventricles and the mitral and aortic valves were examined. The myocardium of the left ventricle was diffusely hypertrophied and the endocardium of the left auricle showed patchy fibrous thickening. Scattered in the left ventricle were occasional stellate scars associated with small amounts of round-cell infiltration. In addition, several minute focal necroses together with a few polymorphonuclear leucocytes and lymphocytes were seen. Similar areas of acute inflammatory reaction were seen in the endocardium of the

left ventricle. There were also small areas of necrosis and fibrinoid degeneration of the endocardium. The small branches of the coronary arteries, however, showed no lesions. No other abnormalities were seen.

CASE 3.—

Clinical History.—H. P. E., a Negro man, aged 25 years, was admitted to the Philadelphia Naval Hospital on Jan. 1, 1945, with a chief complaint of periodic shortness of breath. He had enlisted in the United States Navy on April 4, 1938. The past medical and family histories were not informative. He had no illnesses other than minor infections of the upper respiratory tract before his first admission to the sick list.

On Aug. 8, 1944, while engaged in heavy work on one of the tropical islands in the South Pacific where he had been stationed for several months, he suddenly fell unconscious. He soon regained consciousness, but on admission to the hospital he was objectively dyspneic, and the physical signs were not relieved by the administration of adrenalin and aminophylline. An x-ray film of the chest was normal. He gradually improved, although attacks of dyspnea and cough recurred, and he was evacuated to a hospital in the continental United States. After his arrival, he had no further dyspnea or other symptoms and was discharged to duty on Dec. 24, 1944. The highest blood pressure during this period was 106/70. Six days later, however, paroxysmal dyspnea recurred and he was admitted to this hospital the next day, Jan. 1, 1945.

On admission he was dyspneic, and numerous crackling and sonorous râles were heard over both lungs. The heart was not thought to be enlarged; the rhythm was regular, the rate was 72, and no abnormal sounds were heard. Blood pressure was 98/56. No other physical abnormalities were noted. Within four days, dyspnea at rest subsided, but the exercise tolerance appeared to be less than normal. However, he had no other symptoms until March 7, when he acquired an acute gonococcus urethritis which was satisfactorily treated with penicillin and which did not recur. On March 11, dyspnea while at rest again appeared and edema of the ankles was first observed. From that time until death, symptoms and signs of congestive failure increased in severity, and the heart, by physical and x-ray examination, increased in size. Two days before death he had severe hemoptysis and there were signs of consolidation in both lungs. He died on June 24, 1945.

Laboratory Data.—There were no electrocardiograms on the first admission. On the second admission, repeated electrocardiograms showed constantly changing P-R intervals, T waves varying from flat to the late V type of inversion in all leads, and constantly isoelectric S-T segments. The cardiac rate varied from 66 to 78 (Fig. 3). Blood cultures on Jan. 2, Jan. 8, Feb. 12, and April 16, 1945, were sterile. Except during the episode of urethritis, tests were repeatedly negative for allergy. Other examinations, most of which were repeated on both admissions, were also normal. These included blood Kahns, blood sugar, blood urea nitrogen, urea clearance, blood cholesterol, and total serum protein. Numerous blood smears were negative for malarial parasites and, in wet preparations of the blood, sickling of the red cells was not demonstrated.

Autopsy (No. 45-194).—

Anatomical Diagnosis: There were chronic degeneration and focal scarring of both ventricles of heart; hypertrophy and dilatation of heart; organizing mural thrombi, left ventricle of heart; chronic passive congestion of lungs, liver, spleen, and kidneys; hydropericardium; hydrothorax, bilateral; ascites; peripheral edema; extensive lobular pneumonia.

Body: There were generalized subcutaneous edema, most marked in the dependent parts of the body. On section there were 2,200 c.c. of clear straw-colored fluid in the peritoneal cavity, 200 c.c. in each pleural cavity, and 150 c.c. in the pericardial cavity. The organs all showed extensive chronic passive congestion. Widespread areas of fresh fibrinopurulent exudate were present in both lungs.

Heart: The heart weighed 550 grams. The chambers of the heart were all dilated and filled with clotted blood. In the left ventricle, small gray-red mural thrombi were loosely adherent to the columnae carneae. The endocardium of the left ventricle and left auricle was slightly thickened. The valves were all thin, delicate, and apparently normal. The coronary arteries

were patent and showed only very slight atheromatous changes. The myocardium of both ventricles was pale and flabby, but no focal lesions were seen.

Microscopically, there was patchy hypertrophy of the left ventricle, but in many areas of both ventricles the muscle fibers were small and appeared stretched, and small colorless vacuoles were numerous in the muscle fibers. In some fibers, the vacuoles were so numerous that a honey-comb appearance resulted. The fibrous septa were edematous, and rarely minute collections of lymphocytes, plasma cells, and macrophages were seen. None of these, however, resembled Aschoff bodies. The mural thrombi in the left ventricle were just beginning to organize. In sections of both auricles and of the mitral and aortic valves, no lesions were seen. Special stains for glycogen and fat were not obtained since the only available material was preserved in 80 per cent alcohol. In Gram stains, bacteria were not seen in the thrombi.

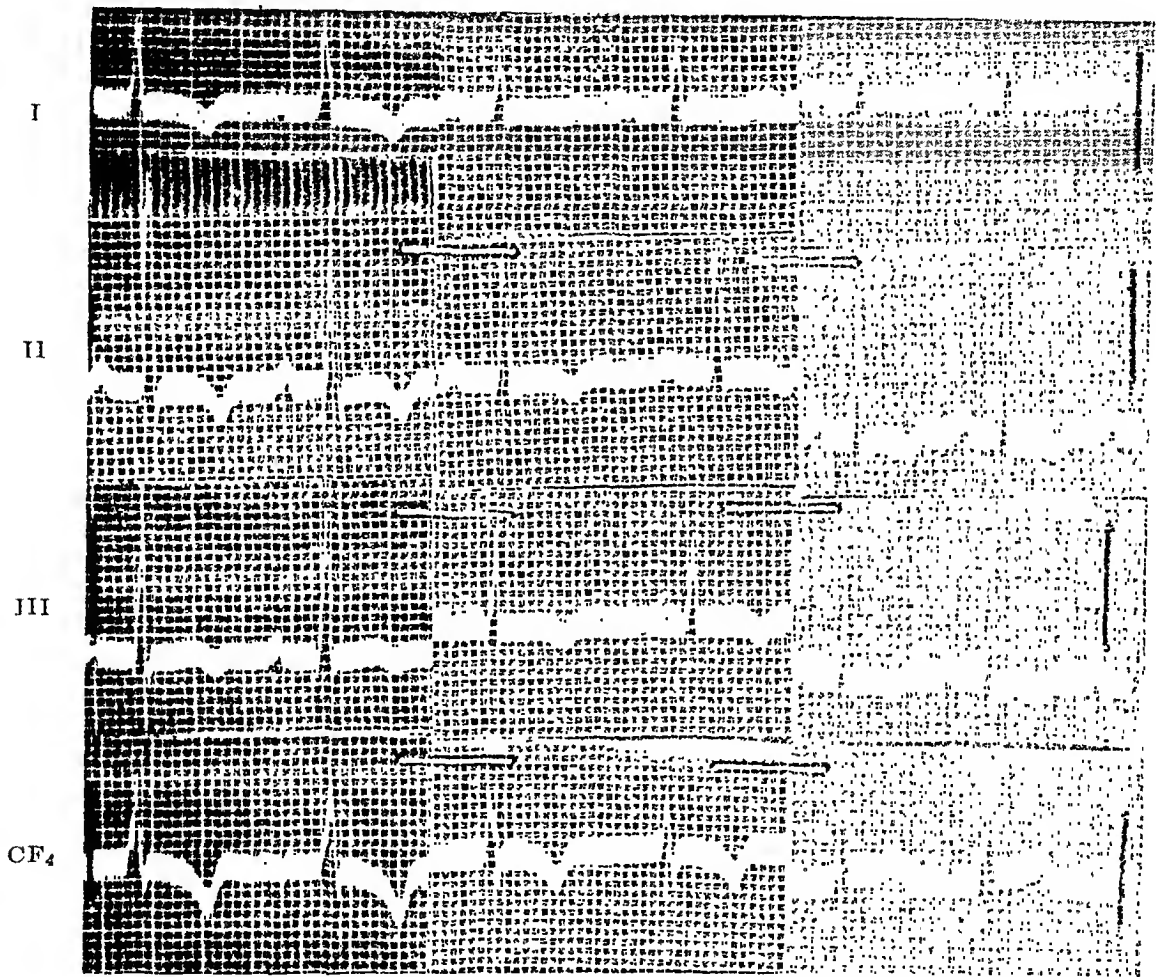


Fig. 3.—Case 3. Throughout the five months of final hospitalization there were constantly changing P-R intervals and varying types of T waves in Leads I, II, and IV, which are shown in the above tracings. The changes in Lead IV may be due to variations in position of the electrodes.

CASE 4.—

Clinical History.—C. W., a white man, aged 29 years, was admitted to the Philadelphia Naval Hospital on June 15, 1945, complaining of vomiting and abdominal pain of four days' duration. The past medical and family histories were irrelevant. He enlisted in the United States Army in August, 1942, and was well until January, 1945, when he was stationed in Oran, Algeria. At that time, he was found wandering about the streets in a state of mental confusion. Upon hospitalization, a diagnosis of amnesia was made, for which he was discharged from the service on April 15, after his return to the continental United States. During this period, an

x-ray film of the chest was reported as normal and the highest blood pressure was 116/80. He then worked as a bellboy until June 11, 1945, when he was taken ill with nausea, vomiting, and cramplike abdominal pains, and was admitted to this hospital four days later.

On admission, he was dyspneic, cyanotic, and jaundiced. There was no peripheral edema, but the superficial veins of the neck were distended. The heart appeared to be moderately enlarged, both on physical and subsequent x-ray examination; the cardiac rate was 120; the rhythm was regular; audible gallop sounds were present; and a soft systolic murmur was localized at the apex. The blood pressure was 90/82. The lungs were not remarkable and the liver and spleen were not at first palpable. Within a day, however, he became mentally confused; numerous crackling râles were heard over both lungs; signs of effusion in the pleural and peritoneal cavities appeared; and the legs became edematous. The jaundice deepened and the liver became palpable. He grew weaker and died on June 24, 1945, nine days after admission.

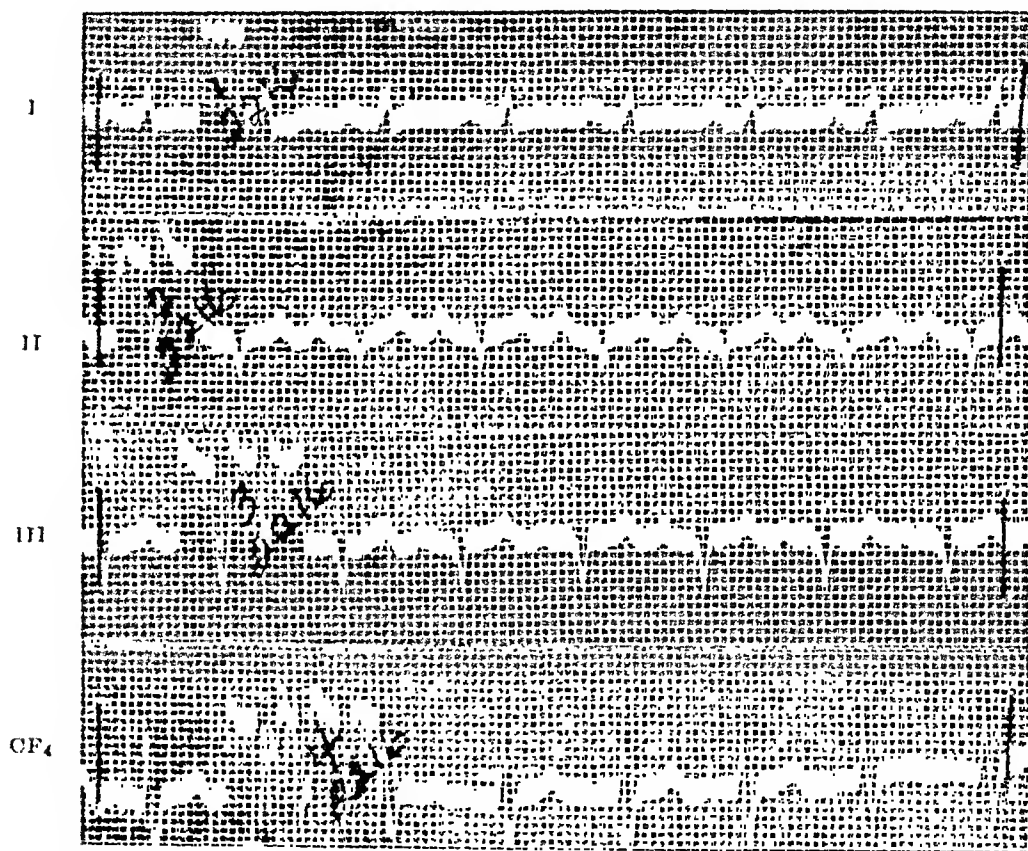


Fig. 4.—Case 4. This tracing taken during the terminal stage of illness shows low voltage QRS complexes in limb leads and the flattened T_1 .

Laboratory Data.—On the first admission, electrocardiograms were reported as normal. During the final hospitalization, an electrocardiogram showed a P-R interval of 0.18 second; a QRS complex of 0.07 second and low voltage throughout; and flattened T waves in all leads (Fig. 4). During the first admission, all laboratory tests were normal including repeated smears for malaria, blood Kahns, blood counts, urinalyses, examination of the spinal fluid, electroencephalogram, blood sugar and urea nitrogen, and several basal metabolic rates. During his final illness, urinalyses showed the presence of bile, traces of albumin, and numerous white blood cells. The blood bilirubin, estimated by the van den Bergh method, was 9 mg. per 100 cubic centimeter. The blood urea nitrogen rose from 18 on admission to 82 mg. per 100 c.c. on the day before death. One blood culture was sterile.

Autopsy (No. 45-197).—

Anatomical Diagnosis: There were chronic degeneration of both ventricles of heart; hypertrophy and dilatation of heart; chronic passive congestion of lungs, spleen, liver, and kidneys; hydrothorax, bilateral; ascites; peripheral edema; jaundice; organizing mural thrombi, left ventricle of the heart; embolic thrombus and infarct of the left kidney; organizing thrombi of the prostatic veins; multiple embolic thrombi of the pulmonary arteries; and multiple infarcts of both lungs.

Body: The lips, mucous membranes, and nail beds were intensely cyanotic. The legs, dependent parts of the body, and the eyelids were edematous. The skin and sclerae were jaundiced. On section, 1,000 c.c. of clear, bile-tinged fluid was present in the abdominal cavity, 1,500 c.c. in the right pleural cavity, and 300 c.c. in the left pleural cavity. The amount of pericardial fluid was not significantly increased. There was marked chronic passive congestion of the organs. A recent small infarct was present in the left kidney. Most of the veins about the prostate were occluded by organizing thrombi. Large hemorrhagic infarcts were present in both lungs and were associated with numerous organizing thrombi in the pulmonary arteries. The liver was markedly engorged with blood and microscopically the central and mid-zonal areas were necrotic and replaced by hemorrhage. Permission was not obtained to examine the brain.

Heart: The heart weighed 450 grams. All of the chambers of the heart were dilated and filled with blood. The left ventricle also was moderately hypertrophied. The valves were all normal. Among the trabeculae of the left ventricle were several small gray-red thrombi which were firmly attached to the underlying endocardium. Elsewhere the endocardium was normal and there were no gross lesions of the myocardium. The coronary arteries were patent and showed only very slight atheromatous changes of the intima.

Microscopically, in sections of both ventricles, groups of muscle fibers, particularly in the left ventricle, were hypertrophied. In most areas, however, the individual fibers were thin and appeared stretched. A few of the hypertrophied fibers contained scattered, clear, colorless elliptical vacuoles within the cytoplasm. This vacuolization was perhaps more conspicuous beneath the endocardium to which were attached the mural thrombi. These thrombi were already deeply invaded by proliferating fibroblasts and lamination was still visible only on the surface. Elsewhere the endocardium was normal. No lesions were seen in either auricle or in sections of the mitral and aortic valves. Since only blocks preserved in 80 per cent alcohol were available, stains for glycogen and fat were unsatisfactory. In Gram stains bacteria were not seen in the thrombi.

DISCUSSION

In a discussion of these cases, it is advisable first to recapitulate the salient clinical features in order to emphasize their differences.

In Case 1, hypertrophy of the heart and symptoms of myocardial insufficiency were first detected soon after an operation for gangrenous appendicitis requiring drainage. Convalescence was complicated only by a respiratory tract infection, thought to be pneumonia, which subsided without the administration of sulfonamides. The patient had no further evidence of infection and was afebrile until shortly before death, when bronchopneumonia occurred. Following discharge from the service, because of enlargement of the heart, for which hospitalization was not considered essential, he was examined frequently as an outpatient, but evidence of congestive failure was not recognized until the final admission to this hospital eighteen months afterward and one month before death. In Case 2, congestive heart failure was not recognized until the final admission a few hours before death. The disorder for which the patient was first admitted to the sick list and for which he was subsequently discharged from the service was un-

explained recurrent hypochromic anemia which always responded promptly to treatment. However, the patient himself related the onset of symptoms to an acute infection of the respiratory tract, but this infection was not observed clinically and he remained afebrile throughout the illness. Laboratory data also did not suggest the presence of infection. At first, in Case 3, the patient was thought to have bronchial asthma, and it is possible that he also had acute bronchitis. Except during the attack of acute urethritis, he had no further evidence of infection and was afebrile until the occurrence of terminal bronchopneumonia. The diagnosis of bronchial asthma was subsequently discarded when no evidence of allergy was demonstrated. For at least six months before death, however, incipient congestive failure was recognized clinically and for this reason he was not discharged from the service. In Case 4, the patient was first hospitalized for amnesia of sudden onset and was subsequently discharged with this diagnosis. Two months later, however, he was admitted to this hospital in severe congestive failure and died nine days later. The clinical course was entirely afebrile and laboratory data did not suggest the presence of an infectious disease.

At this point, parenthetically, it is worthy of emphasis that at autopsy the mural thrombi in the left ventricles of Cases 3 and 4 did not resemble the vegetations of bacterial endocarditis. Grossly the surfaces were smooth. The deeper layers, microscopically, were being replaced by fibroblasts and the superficial layers were laminated and not necrotic. Bacteria could not be demonstrated with Gram stains. It is evident, therefore, that only in Case 1 was the onset of symptoms related to the occurrence of an acute infectious disease and in none of the cases was there evidence of any chronic infection. It is equally apparent that the onset of illness and clinical course in each case differed and did not at first suggest a diagnosis of heart disease.

It is interesting that in each patient serious heart disease was not at first recognized as the outstanding abnormality. Only in Case 1 was the diagnosis made early and then only after the patient was discharged to duty following recovery from the appendectomy. In patients of this age, without hypertension or evidence of valvular disease, a diagnosis of heart disease is not ordinarily a prominent consideration. However, in all cases, a thorough survey of the heart was actually made early in the course of the illness. That tests, including electrocardiograms and chest x-ray films, at first gave normal results, except in Case 1, probably explains why a diagnosis of heart disease was temporarily discarded.

The question arises, therefore, when during the illness of each patient heart disease may have occurred. In Case 1, the heart was reported as being enlarged by x-ray examination during convalescence from the appendectomy. This was confirmed during the second admission, but at that time an electrocardiogram was said to be normal. It is quite possible, therefore, that cardiac enlargement may have preceded the appendicitis. In Case 2, enlargement of the heart by x-ray examination and electrocardiographic changes suggestive of myocardial damage were first recognized six to eight months following the onset

of symptoms. There is a distinct possibility, however, that at the time of the first admission, when cough, weakness and dyspnea on exertion were conspicuous symptoms, the patient was already suffering from heart disease. It is also probable that in Case 3, heart disease was responsible for the paroxysmal attacks of cough and dyspnea which at first were diagnosed as bronchial asthma. In Case 4, likewise, the sudden onset of mental confusion less than six months before death may have been caused by emboli from an already damaged heart. In this connection, it will be recalled that at autopsy the mural thrombi in the left ventricle were already extensively organized. From the available evidence, therefore, it is possible that heart disease in all four cases already existed at the time of the first admission to the sick list.

There appears to be little doubt, pathologically, that the principal cause of death in all four cases was congestive heart failure. In the first place, the hearts weighed 890, 560, 550, and 450 grams, respectively. These weights are obviously greater than the limits of normal. In the second place, evidence of marked chronic passive congestion was widespread both grossly and microscopically. In Cases 1 and 3, however, the final illnesses were complicated by terminal bronchopneumonia. Multiple pulmonary emboli and infarcts in Cases 2 and 4 were undoubtedly manifestations of peripheral stasis and thrombosis incident to the congestive failure and almost certainly were important causes in precipitating death.

The jaundice and necrosis of the parenchymal liver cells in Case 4 may have been due to chronic passive congestion and to the destruction of excessive amounts of red blood cells in the pulmonary infarcts, or, to these factors plus an acute infectious hepatitis; the associated uremia was distinctly terminal.

In Cases 3 and 4, the presence of mural thrombi in the left ventricles suggests myocardial infarction, but the coronary arteries grossly and microscopically were not occluded and even microscopically there were no large areas of necrosis. It is much more likely that a combination of stasis of blood flow in the ventricles and small areas of subendocardial degeneration was responsible for these lesions.

As for etiology, it is apparent from the case reports that none of the factors commonly responsible for hypertrophy and dilatation of the heart were present. Thus, there was no evidence of hypertension, coronary arteriosclerosis or thrombosis, valvular disease, congenital defects of the heart, or chronic disease of the lungs. There was no evidence of hyperthyroidism, clinically or pathologically. As far as can be determined, the diets of the patients were adequate and in some instances were supplemented with multiple vitamin preparations. It is very unlikely, therefore, that any of them were suffering from vitamin B deficiency. The possibility of rheumatic myocarditis without valvulitis was considered, but the clinical manifestations of rheumatic fever were lacking and the small foci of round-cell infiltration in the ventricles of Cases 2 and 3 did not resemble Aschoff bodies.

In Case 2, there was recurrent, moderately severe anemia, which was the presenting symptom during most of the illness. It was classified only as being

hypochromic and the etiology was not determined. The response to therapy was prompt, however, and the patient was not severely anemic at death. There is great doubt, therefore, whether an anemia of this extent so affected the heart as to cause hypertrophy and congestive failure. White⁵ believed such anemias to be without effect in permanently damaging the heart unless they were severe or prolonged. Nemet and Gross⁶ found cardiac hypertrophy to be extremely rare in anemia. Amadeo⁷ was equally impressed by the failure of anemia to produce cardiac hypertrophy.

Recently Candel and Wheelock⁸ have emphasized the frequency with which acute infections, particularly of the respiratory tract, may be complicated by transient acute myocarditis and have described the electrocardiographic changes which are thought to indicate derangement of the myocardium. But in our cases electrocardiograms were not significantly abnormal early in the illnesses. However, the onset of symptoms in Case 1 did immediately follow an acute infection. Undoubtedly, the remaining patients had upper respiratory tract infections from time to time before the onset of the final illness, but these must have been so mild that hospitalization was unnecessary. The attack of urethritis in Case 3, moreover, occurred long after the onset of cardiac symptoms and, although it may have adversely affected the course of the illness, it certainly was not the cause of it. It is possible that the apparent myocardial damage described by Candel and Wheelock⁸ may not always be reversible and may cause cardiac hypertrophy some time afterward; but this concept is so unusual that it can be considered only as a possibility at this time.

Although the present cases are not typical of so-called isolated myocarditis of Fiedler⁹ in which extensive inflammation of the myocardium is characteristic, there are points of similarity between the two groups which might justify this classification of our cases. As in isolated myocarditis, so in the present cases, relatively rapid and progressive enlargement of the heart terminated in congestive failure, but evidence of chronic infection was lacking.

In Cases 2 and 3, there were minute, although rare, foci of inflammation in the myocardium, and in Cases 3 and 4, there was also extensive focal vacuolization of the myocardium of the ventricles. These were not so extensive, however, as to constitute an unequivocal diffuse myocarditis, and in Case 1 there was neither vacuolization nor inflammatory exudate. In this case, furthermore, the scarring was no more extensive than is customarily observed in myocardial hypertrophy of this degree from any common cause. Nevertheless, it may be argued that extensive inflammatory exudate was present in the myocardium of the present cases earlier in the course of the disease and had largely disappeared by the time of death. Even if these cases are thought to belong in this group, therefore, one is still far from any conclusion as to etiology. In his recent reviews of the literature, Saphir^{10,11} has pointed out not only the variability of extent and character of the inflammatory exudate in the hearts of the reported cases of isolated myocarditis, but also the large number of infections which have been suggested as dubious causes of the disease. Fiedler's myocarditis, consequently,

appears to be a group which includes various disease entities, the etiology of which is just as uncertain as that of the present cases.

It is unfortunate that properly fixed material was not available for glycogen or fat stains in Cases 3 and 4. Although it is highly unlikely that the vacuoles in the muscle fibers were glycogen, or that these cases represent some phase of glycogen-storage disease, it would be satisfying to settle this question. If the lesions were either fatty or hydropic degeneration, as seems more likely, such abnormalities are not specific of any disease entity. Interestingly enough, one of Levy and Rousselot's¹ cases also had extensive vacuolization of the myocardium which was interpreted as hydropic degeneration.

From the preceding discussion, it is evident, therefore, that the cause of the myocardial hypertrophy in each of the four cases presented is obscure, and etiologically these cases may be wholly unrelated.

SUMMARY

1. Four fatal cases of unexplained hypertrophy and dilatation of the heart during the third decade of life are presented. None of the usual causes of hypertrophy were present.

2. The onset of illness differed in individual cases and was not at first recognized as heart disease.

3. Electrocardiograms at first were normal. When changes occurred, the abnormalities suggested only nonspecific myocardial damage.

4. The possible etiologic factors are discussed, but it is not concluded which, if any, were responsible for the cardiac hypertrophy.

5. There is no certainty that the causes of heart disease in the four cases were related.

REFERENCES

1. Levy, R. L., and Rousselot, L. M.: Cardiac Hypertrophy of Unknown Etiology in Young Adults, *AM. HEART J.* 9: 178, 1933.
2. Whittle, C. H.: "Idiopathic" Hypertrophy of the Heart in a Young Man, *Lancet* 216: 1354, 1929.
3. Laubry, C., and Walser, J.: Sur un cas d'insuffisance cardiaque primitive: les myocardies, *Bull. et mém. Soc. méd. d. hôp. de Paris* 49: 409, 1925.
4. Levy, R. L., and von Glahn, W. C.: Cardiac Hypertrophy of Unknown Etiology in Adults, *Tr. A. Am. Physicians* 52: 259, 1937.
5. White, P. D.: "Heart Disease", ed. 2, New York, 1937, The MacMillan Co., p. 389.
6. Nemet, G., and Gross, H.: Cardiac Hypertrophy in a Case of Cooley's Anemia, *AM. HEART J.* 12: 352, 1936.
7. Amadeo, J. A.: Un Nuevo Fenomeno Cardiologico observado entre los Campesinos Puertorriqueños; Analizado a Traves de los Llamados Soplos Hemicos; Y una Nueva Teoria que de una Explicacion Fisio-Anatomica Razonable de Esta, *Bol. Asoc. méd. de Puerto Rico* 37: 161, 1945.
8. Candel, S., and Wheelock, M. C.: Acute Non-Specific Myocarditis, *Ann. Int. Med.* 23: 309, 1945.
9. Fiedler: Ueber akute interstitielle Myocarditis, in *Festschrift des Stadtkrankenhauses, Dresden, 1899, Friedrichstadt*; cited by Saphir (1941).
10. Saphir, O.: Myocarditis (A General Review, With Analysis of Two Hundred Forty Cases), *Arch. Path.* 32: 1000, 1941.
11. Saphir, O.: Myocarditis (A General Review, With Analysis of Two Hundred Forty Cases), *Arch. Path.* 33: 88, 1942.

PARENTERAL VITAMIN B AS AN AGENT FOR DETERMINING THE ARM-TO-TONGUE CIRCULATION TIME

PART I

ROY E. SWENSON, M.D

PITTSBURGH, PA.

PREVIOUS observations on the velocity of blood flow have been made by using saccharine,⁴ calcium salts and magnesium sulfate,⁸ and decholin³ to determine the arm-to-tongue circulation time. Sodium cyanide¹² and alpha lobeline^{2,5,10,11} have been used to measure the circulation time from the arm to the carotid sinus. Ether^{2,7} has been used to determine the circulation time from the arm to the lung. Papaverine⁵ has been utilized to measure the circulation time from the arm to the central nervous system.

The arm-to-tongue circulation time is of clinical value⁸ in the diagnosis of congestive heart failure and of those diseases in which the venous return is obstructed. It is also of value in those diseases where the velocity of the blood flow is increased, as in the anemias, hyperthyroidism, and certain febrile states.

Hussey, Cyr, and Katz⁸ have summarized the requirements for a suitable agent for determining the circulation time as follows:

1. It must be nontoxic in the dosage used.
2. It must have no undesirable effect upon the condition being studied.
3. There must be a minimum of unpleasant side effects.
4. It must be eliminated rapidly so that it can be used repeatedly.
5. It must have an end point that is easily recognized by the patient.
6. It should be readily available at a low price.

The results of the work to be reported indicate that the vitamin B complex when given intravenously meets all of these conditions.

The use of the vitamin B complex as an agent to determine the arm-to-tongue circulation time was suggested when the complex was given intravenously to an obstetric patient three days post partum. She complained of a taste on her tongue similar to that of a "chewed-up vitamin tablet." The complex was then given to other patients who also tasted it. These observations led to further study of its value in estimating circulation time.

Received for publication March 12, 1946.
From the Mercy Hospital.

The preparation used in this study had the following composition*:

Thiamine hydrochloride	10.0 mg.
Riboflavin	10.0 mg.
Pyridoxine hydrochloride	5.0 mg.
Calcium pantothenate	50.0 mg.
Nicotinamide	250.0 mg.

These amounts were contained in 5.0 c.c. of sterile isotonic saline solution. Five cubic centimeters were used for each determination. A duplicate determination was made within a few seconds of the initial one. Each subject, therefore, received a total of twice the amount of the drugs listed.

The normal serum concentration of thiamine hydrochloride is from 0.2 to 2.0 μ g per 100 c.c.,¹⁴ and the intravenous administration of 50 mg. of the substance elevates this level to from 130 to 200 μ g within five minutes. This falls to from 5 to 15 μ g within an hour, for the substance is almost immediately excreted. Large doses have been given to rats and dogs without any toxic effect being noted in the electrocardiograms.⁶ From 26 to 68 per cent of a 16 mg. test dose of riboflavin given intravenously is excreted within four hours, and there is little storage of the substance.^{13,14} Pyridoxine hydrochloride and calcium pantothenate are rapidly excreted.^{16,17} The intravenous administration of 5 mg. of nicotinic acid per kilogram in man increases the normal whole blood concentration from 0.25 to 0.89 mg. per 100 c.c. to a maximum of 130 mg. per cent; this falls to normal in two hours as conjugates are excreted in the urine.^{14,18} In the literature reviewed, no variations in the pulse or blood pressure were reported after the administration of these substances in the dosages given.

TECHNIQUE

The patient was placed in a semirecumbent position and the left arm was supported at the approximate level of the right auricle. A tourniquet was then applied above the antecubital fossa. Sterile 10 c.c. syringes and No. 20 needles were used. After the needle was inserted into one of the antecubital veins, the tourniquet loosened, and venous flow re-established, 5 c.c. of the solution were rapidly injected. Time was started on a stop watch at the beginning of the injection. When the patient stated that he tasted the substance, time was stopped, but the needle was left in the vein. When he no longer tasted the substance, a duplicate determination was made and the needle removed.

The taste on the tongue was described as follows:

1. A taste like that of a brewers' yeast tablet.
2. A taste similar to that of a vitamin tablet.
3. A stale, fishy taste and odor.
4. A warm sensation on the tongue and in the throat.

Interns and nurses who received the substance stated that the taste and odor were unmistakable and that the onset of the taste was abrupt and intense.

*The commercial preparation, "Solu-B," manufactured by The Upjohn Co., Kalamazoo, Mich., was used. The Upjohn Company generously supplied the Solu-B used in this work.

RESULTS

Obviously this test would have more practical value and the observations reported would be of greater scientific interest if it could be established that a single component produces the taste sensation. Further study of this aspect of the problem is in progress.

Arm-to-tongue circulation times were determined on fifty normal subjects from various age groups. No circulatory abnormalities were recognized or suspected in any of them. Table I summarizes the control group. The average times of the fifty control subjects as a single group varied from 9.8 to 10.3 seconds for the initial and duplicate determinations, respectively.

TABLE I. AVERAGE ARM-TO-TONGUE CIRCULATION TIMES OF NORMAL CONTROLS

NUMBER OF PATIENTS	AGE GROUP IN YEARS	CIRCULATION TIME IN SECONDS		DEVIATIONS IN SECONDS	
		FIRST	DUPLICATE	FIRST	DUPLICATE
16	16-30	8.7	9.7	-2, +4	± 3
16	30-40	10.1	10.5	± 4	± 4
18	40-	10.7	10.7	± 3.3	± 3

Estimates of circulation time were made on fifty-two patients with cardiac disease. The cases were studied in four groups. Table II summarizes the results obtained in three groups in which congestive failure was present. Table III summarizes the fourth group in which there was heart disease without congestive failure.

TABLE II. AVERAGE ARM-TO-TONGUE CIRCULATION TIMES OF PATIENTS WITH CONGESTIVE FAILURES

NUMBER OF PATIENTS	DISEASE PROCESS	CIRCULATION TIME IN SECONDS		DEVIATIONS IN RANGE IN SECONDS	
		FIRST	DUPLICATE	FIRST	DUPLICATE
15	Congestive failure; no treatment	34.8	34.6	28-53	27-49
14	Congestive failure; digitalized but not controlled*	22.7	23.1	14.1-46.7	13.5-39.9
10	Congestive failure; digitalized and controlled†	11.8	11.8	9.8-13.4	9.0-15.1

*Patients had received only 0.7 Gm. of digitals.

†Patients had received at least 1.4 Gm. of digitals.

TABLE III. ARM-TO-TONGUE CIRCULATION TIMES OF PATIENTS WITH CARDIAC DISEASE BUT WITHOUT CONGESTIVE HEART FAILURE

CASE	DISEASE	CIRCULATION TIME	
		FIRST	DUPLICATE
1	S. B. E.; mitral stenosis	10.1	10.2
2	S. B. E.; mitral stenosis	12.5	14.3
3	Hypertension	9.9	10.8
4	Constrictive pericarditis, after pericardiectomy	12.2	10.0
5	Hypertension; auricular fibrillation	17.0	21.5
6	Coronary occlusion after two weeks	10.0	10.0
7	Hypertensive heart disease; cerebrovascular accident	16.2	15.6
8	Hypertensive encephalopathy; hypertension	9.1	9.4
9	Coronary occlusion	20.0	23.4
10	Arteriosclerosis heart disease; auricular fibrillation; digitalized	10.3	11.0
11	Arteriosclerosis, hypertension; auricular fibrillation; ventricular aneurysm	19.2	16.8
12	Hypertension; aortic stenosis	10.5	12.0
13	Arteriosclerosis; auricular fibrillation	31.0	32.5

The longest circulation times were recorded in those patients in whom congestive failure was severe and untreated. The times were also increased in those patients whose failure had been treated but not controlled. Those who were treated and whose failure had been clinically controlled had times that approached the normal range, although few were actually within normal limits.

Patients who received this vitamin B preparation had few side reactions. Two complained of epigastric fullness, and four stated that they felt unusually warm. One patient complained of bladder tenesmus twenty-four hours after the injection. No other side effects were noted.

SUMMARY

1. The arm-to-tongue circulation time using parenteral vitamin B as the test agent has been determined on fifty normal subjects. In this control group the average time was found to vary from 9.8 to 10.3 seconds for the initial and duplicate determinations, respectively.

2. Similar determinations were also made on a group of fifty-two patients with cardiac disease. It was found that the circulation times determined by this method parallel the times reported for other test agents.

3. The vitamin B preparation used appears to be nontoxic, has little effect upon circulatory dynamics, is readily available, is eliminated rapidly, and has an abrupt end point. The side reactions are minimal. This preparation, therefore, meets the requirements for a satisfactory agent for the determination of the arm-to-tongue circulation time.

4. Studies are now being made to determine which components of the B complex are responsible for the distinctive end point.

Appreciation is expressed to Dr. W. L. Mullins, cardiologist of the Mercy Hospital, Pittsburgh, Pa., for many helpful suggestions.

REFERENCES

1. Baer, S., and Isard, H. J.: Value of Ether Circulation Time in the Diagnosis of Right Heart Failure, *Am. J. M. Sc.* 200: 209, 1940.
2. Berliner, K.: Use of Alpha Lobeline for Measurement of the Velocity of the Circulation, *Arch. Int. Med.* 65: 896, 1940.
3. Cotrell, J. D., and Cuddie, D. C.: Arm to Tongue Circulation Time in Chronic Asthma, *Brit. M. J.* 1: 70, 1942.
4. Duras, F. P.: Measurement of the Circulation Time With Saccharin, *Lancet* 1: 303, 1944.
5. Elek, S. R., and Solarz, S. D.: Use of Papaverine as an Objective Measure of the Circulation Time, *AM. HEART J.* 24: 821, 1942.
6. Haynes, F. W., and Weiss, S.: Responses of the Normal Heart and the Heart in Experimental Vitamin B₁ Deficiency to Metabolites (Pyruvic Acid, Lactic Acid, Methyl Glyoxal, Glyceraldehyde and Adenylic Acid) and to Thiamine, *AM. HEART J.* 20: 34, 1940.
7. Hitzig, W. M.: The Use of Ether in Measuring the Circulation Time From the Antecubital Veins to the Pulmonary Capillaries, *AM. HEART J.* 10: 1080, 1934.
8. Hussey, H. H., Cyr, D. P., and Katz, S.: Comparative Value of Calcium Gluconate, Magnesium Sulfate, and Alpha Lobeline as Agents for the Measurement of the Arm to Tongue Circulation Time in Fifty Patients With and Fifty Patients Without Heart Failure, *Ann. Int. Med.* 17: 849, 1942.
9. Hussey, H. H., Wallace, J. J., and Sullivan, J. C.: Value of Combined Measurements of Pressure on the Arm to Tongue and Arm to Lung Circulation Times in the Study of Heart Failure, *AM. HEART J.* 23: 22, 1942.
10. Lillienfeld, A., and Berliner, K.: Duplicate Measurements of the Circulation Time Made With Alpha Lobeline Mixture, *Arch. Int. Med.* 69: 739, 1942.
11. Piccione, F. V., and Boyd, L. J.: Determination of Circulatory Velocity by Alpha Lobeline, *J. Lab. & Clin. Med.* 26: 766, 1944.
12. Reingold, I. M., Neuwelt, F., and Necheles, H.: Circulating Time (Sodium Cyanide Method) in Human Beings and the Dog as Affected by Fasting and by Meals, *J. Lab. & Clin. Med.* 28: 812, 1943.
13. Goodman, L., and Gilman, A.: *The Pharmacological Basis of Therapeutics*, 1941, The Macmillan Co., New York, pp. 12, 54, 1259.
14. Cantarow, A., and Trumper, M.: *Clinical Biochemistry*, ed. 3 (revised), Philadelphia and London, 1945, W. B. Saunders Co., pp. 314-331.
15. Field, H., Melnick, D., Robinson, D., and Wilkinson, C. F.: Studies on the Chemical Diagnosis of Pellagra, *J. Clin. Investigation* 20: 379, 1941.
16. *The Physiological Activity and Experimental Clinical Use of Vitamin B₂*, Rahway, N. J., 1941, Merck & Co., Inc.
17. *The Physiological Activity and Experimental Clinical Use of Pantothenic Acid*, Rahway, N. J., 1941, Merck & Co., Inc.
18. *The Physiology and Clinical Use of Nicotinic Acid and Nicotinamide*, Rahway, N. J., 1940, Merck and Co., Inc.

THE COMBINED USE OF LANATOSIDE C AND QUINIDINE SULFATE IN THE ABOLITION OF ESTABLISHED AURICULAR FLUTTER

RALPH M. TANDOWSKY, M.D., JOSEPH M. OYSTER, M.D., AND
ALEXANDER SILVERGLADE, M.D.
LOS ANGELES, CALIF.

DIGITALIS leaf and quinidine have been recommended, singly and in combination, for the abolition of auricular flutter.¹ We have not obtained consistent results by this method of therapy. One reason is that this arrhythmia frequently undergoes spontaneous reversion to a normal mechanism in both treated and untreated cases. In a study embracing the use of these drugs, this clinical inconsistency may be greatly obviated by using as test subjects patients with established auricular flutter who have failed to respond to various methods of therapy for a period of not less than three days. Furthermore, a better pharmacologic understanding of both quinidine and digitalis is essential so that the careful choice of each in proper dosage and sequence will result in therapeutic effectiveness. Heretofore, with the exception of auricular fibrillation, the use of drugs in the conversion of the various arrhythmias has not been based upon sound therapeutic principles.

The action of both quinidine and digitalis on the heart muscle and its neuromechanism is varied and not without complicating factors. Quinidine, for example, reduces vagal tone indirectly, while its direct effect is to depress conduction in auricular muscle. Thus, indirectly it improves conduction and directly this function is depressed; its paralyzing action on the vagus nerve improves conduction, while its action on the auricular muscle increases the refractory period, thus prolonging the duration of the circus wave. A-V conduction under its influence may be variable.² This variability of quinidine action has led many to recommend digitalis as the preferable drug in the treatment of supraventricular tachycardia.³ It is through effects such as these that quinidine slows the circus rate in auricular fibrillation.^{4, 5} Its action when a mechanism other than auricular fibrillation is present is difficult to predict. This leads us to believe that the use of quinidine in the treatment of auricular flutter is unsound therapy, while in the presence of auricular fibrillation its value has been clearly established.

Digitalis, on the other hand, exerts a stimulating vagus effect⁶ which shortens the refractory period. Its direct muscular action slows conduction in auricular muscle by increasing the refractory period. Vagal action is more marked than the direct effect on the auricular musculature and the usual result, therefore, is

From the Department of Medicine of the College of Medical Evangelists and the Medical Service of the Los Angeles County General Hospital.

Received for publication Nov. 14, 1945.

an increase in the rate and irregularity of the circus movement. In addition to its effect on the vagus and the auricles, digitalis produces a slowing effect on the ventricles by direct and indirect depression of the A-V node. The combined effects of digitalis are an effect on the refractory period of auricular muscle, which acts toward converting auricular flutter into auricular fibrillation, and depression of A-V conduction.⁶

Lanatoside C,* by its strong vagus influence, in our experience has been especially effectual in slowing the heart rate. Its rapidity of action, in our opinion, accounts for its strong vagus effect, and this action is far superior to other forms of digitalis in common use.⁷ Rapid slowing of the ventricular rate has been the rule in the presence of auricular flutter when lanatoside C is used; of especial interest has been our frequent observance of the conversion of auricular flutter to auricular fibrillation following this slowing effect. When slowing of the heart rate and restoration of normal rhythm occurs, we may attribute this effect to the combined action of digitalis upon the auricular muscle and nodal tissue.⁹

Digitalis, particularly when given by the oral route, often fails to produce effective cardiac response in the presence of auricular flutter and other supra-ventricular arrhythmias, particularly in the presence of congestive heart failure.¹⁰ Improper assimilation from a digestive tract is probably the causative factor.

Lanatoside C, when given intravenously, has many advantages over oral digitalis, particularly if immediate action is essential. We have demonstrated its rapid action in auricular flutter, clinically and electrocardiographically, in those with and without congestive heart failure.¹⁰ Lanatoside C, when given intravenously, will, on occasion, convert auricular flutter to sinus rhythm. This conversion, however, is inconsistent when this arrhythmia has obtained for many days. Conversion of auricular flutter to auricular fibrillation by the intravenous use of lanatoside C is seen quite consistently in those patients whose auricular flutter has been established for three or more days. Once auricular fibrillation makes its appearance, the use of quinidine may be of definite therapeutic value for the conversion of the arrhythmia to sinus rhythm. Lanatoside C may be given in full therapeutic dosage, quickly, by the intravenous route, with a minimum of untoward symptoms.^{11, 12} It has also been shown to be of value prophylactically when sinus rhythm returns.¹³

METHOD AND PROCEDURE

This study embraces the use of both lanatoside C and quinidine sulfate in sequence. Lanatoside C was given intravenously in full digitalizing dosage (1.6 mg.). The effects were maintained by the administration of 1 mg. daily. Quinidine sulfate was used in varying dosage, depending upon individual requirements and tolerance (.72 to 1.44 Gm.).

After the diagnosis of auricular flutter was established clinically and electrocardiographically, historical data were carefully studied to determine the quantity and type of previous medication. Patients who received digitalis in appreci-

*Commercially marketed as Cedilanid by the Sandoz Chemical Works, Inc., New York, N. Y.

able quantities just prior to admission were eliminated from the series. The subjects included in this study were chosen irrespective of age, sex, race, and complicating disease. All were hospitalized. Following the intravenous administration of lanatoside C, frequent serial electrocardiograms were obtained, and clinical examination was made at frequent intervals. As soon as the diagnosis of auricular fibrillation was established, quinidine sulfate was given orally with a maintenance dosage of lanatoside C. When sinus rhythm was established, the quinidine was discontinued but the prophylactic dosage of lanatoside C was continued. In some of the group, other forms of supportive therapy were used, depending upon the underlying symptoms and disease.

RESULTS

Sixteen men and five women constituted the series of patients studied (Table I and Figs. 1, 2, 3, and 4). The diagnosis of auricular flutter was clearly established by the electrocardiograph in all twenty-one patients. The ventricular rates ranged from 140 to 200 per minute. The duration of auricular flutter prior to admission varied from three to twenty-eight days, with an average pretherapeutic duration of approximately fifteen days. This computation had to be based mainly upon information given by the patients and may not be entirely reliable. The age of the twenty-one patients ranged from 30 to 75 years. The average age was 57 years.

Three of the twenty-one patients showed no evidence of pre-existing disease. In the remaining eighteen patients there was associated disease which was diagnostically classified as hypertensive cardiovascular disease in nine patients, rheumatic heart disease in four, arteriosclerosis in two, thyrotoxicosis in one, coronary atherosclerosis in one, and alcoholism with complicating bronchopneumonia in one. In three patients, early congestive heart failure was evident.

Twelve of the twenty-one patients had received no specific therapy. Four of the entire group had received full doses of digitalis and had received maintenance doses of this drug for a number of weeks before the present study was undertaken. Three patients had received digitalis and quinidine, and two had received quinidine alone. None of these nine treated patients had been helped by the therapy they had received.

Following the intravenous administration of lanatoside C to the twenty-one patients under observation, a primary slowing of the ventricular rate occurred within one hour. In four, the primary slowing of the ventricular rate was lacking. In one of these four patients, a slow sinus rhythm was established within twenty minutes. In four of the entire group, sinus rhythm was established without any medication other than the initial dosage of lanatoside C. The time needed for this conversion varied from twenty to sixty minutes. Auricular fibrillation was established after the administration of lanatoside C in fifteen of the group in from two to seventy-two hours. In one patient auricular flutter continued for thirteen days before auricular fibrillation was established. In one patient the flutter was not converted to either auricular fibrillation or sinus rhythm. This patient suffered from thyrotoxicosis and was eventually treated by surgery.

TABLE 1. Results of Treatment of Patients with Ankylosing Spondylitis by the Combined Use of L.A.S. and Quinidine Sulfate in the Treatment of the Cardiovascular System

CASE	AGE	SEX	MEDICATION		SYMPTOMS		PREVIOUS MEDICATION	EFFECT OF PREVIOUS TREATMENT	LAVOSIDE C DOSAGE IN MG.	LAVOSIDE C RESULT		ORAL QUINIDINE DOSAGE	QUINIDINE RESULT	FOLLOW-UP THERAPY	REMARKS		
			CLINICAL	ECG	DURATION	SIGN				COEF.	IMMED.					LATENT	
1 (W. R.)	64	M	H.C.v. D.	A.F.; V.R., 200	14 days	Dysp., palp.	L.H.F. (Early)	Dig. leaf, 20 gr.	None	1.6 I.V. plus 1 mg. daily	None	A. Fib. in 140 min.	None	S.R. in 96 hr	Dig. leaf, 1 1/2 gr daily	C.H.F. improved	10 mo later with gangrene of leg; expired 23 days later from C.V.A.
2 (G. B)	67	M	H.C.v. D.	A.F.; V.R., 140	16 days	Palp.	Tachy.	None	None	1.6 I.V. plus 1 mg. daily	Ventricular rate slowed	S.R. in 50 min.	None	None	Lenat. C, 1 1/2 mg. daily	Good	Seen 6 mo. later with mild C.H.F.; improved with 1 mg. lenat. C daily
3 (L. M.)	45	M	H.C.v. D.	A.F.; V.R., 140	12 days	Dysp.; palp.	Tachy., Br. Asth.	Dig. leaf, 24 gr.; quinidine, 60 gr.	Nausea and cinchonism	1.6 I.V. plus 2 mg. daily	Ventricular rate slowed	A. Fib. in 72 hr.	None	S.R. in 24 hr.	Lenat. C, 1 mg. daily	Good	Follow-up treatment for Br. Asth.
4 (J. McC.)	58	M	R.H.D.	A.F.; V.R., 170	16 days	Dysp.	L.H.F.	Dig. leaf, 12 gr.	Nausea	1.6 I.V. plus 1 mg. daily	Ventricular rate slowed	A. Fib. in 12 hr.	None	None	Dig. leaf, 1 1/2 gr. daily	Partial conversion	A. Fib. continued until discharged 1 wk. later
5 (L. G.)	30	M	Thyrotox.	A.F.; V.R., 140	24 days	Dysp.; palp.	L.H.F. (Mild)	Lugol's solution; deracil. quinidine, 72 gr.	None	1.6 I.V. repeated in 3 days; then 1 mg. daily	None	None	None	None	Surgical	Non-therapeutic	Thyrotoxic; resistant to lenat. C and quinidine
6 (V. R.)	51	F	R.H.D.	A.F.; V.R., 150	3 days	Dysp.; palp.; cough	C.H.F. (Early)	None	None	1.6 I.V. plus 1 mg. daily	Ventricular rate slowed	A. Fib. in 24 hr.	None	S.R. in 12 hr.	Lenat. C, 1/2 mg. daily	Good	None

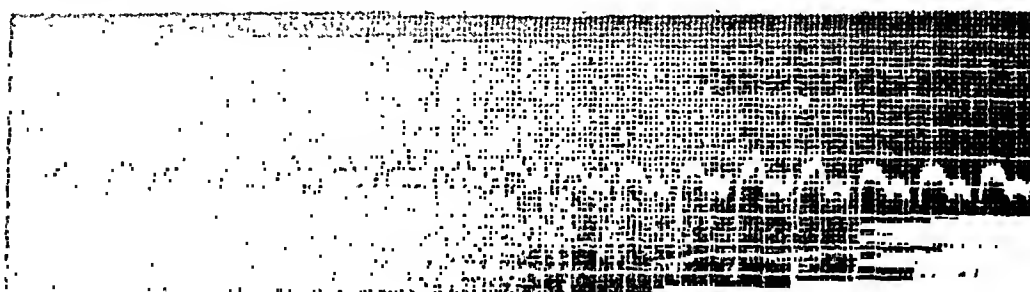
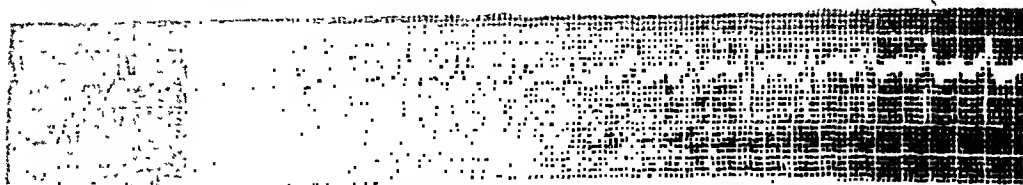
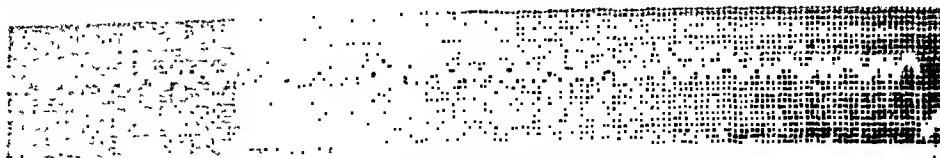
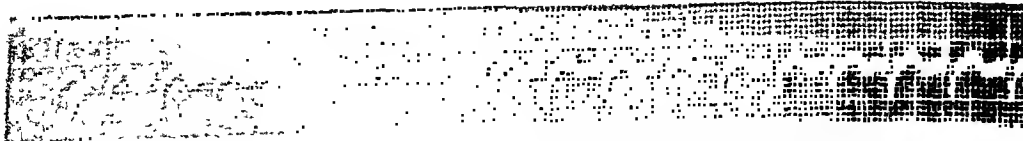
7 (E. M.)	76	F	H.Cv. D.	A.Fl.; V.R., 152	16 days	P. pain; dysp.; palp.	Coron. sel.	Nitro- glycer- ine, P.R.N.	Relief of pain	1.6 I.V. plus 1 mg. daily	Ventricu- lar rate slowed	A. Fib. in 20 hr.	20 gr. daily	None	S.R. in 32 hr.	Lanat. C, 1 mg. daily	Good	14 mo.	Expired, 14 mo. after therapy from C.V.A.
8 (M.S.)	51	M	None	A.Fl.; V.R., 160	17 days	Palp.	Tachy.	Quinidine, 120 gr.	None	1.6 I.V. plus 1 mg. daily	S.R. in 20 min.	None	None	None	None	Lanat. C, 1 mg. daily	Good	34 mo.	This patient had many attacks of A. Fl. previous to the in- stitution of treat- ment
9 (A. H.)	49	F	R.H.D.	A.Fl.; V.R., 152	15 days	Palp.; dysp.	Mit. Sten., C.H.F. (mild)	Dig. leaf, 22 gr.	None	1.6 I.V. plus 1 mg. daily	Ventricu- lar rate slowed	A. Fib. in 2 hr.	20 gr. daily	None	S.R. in 36 hr.	Lanat. C, 1 mg. daily	Good	26 mo.	None
10 (A. K.)	45	M	R.H.D.	A.Fl.; V.R., 200; V.P.C.	12 days	Palp.; P. pain	C.H.F.	Quinidine, dig. leaf (quantity un- known)	None	1.6 I.V. plus Dig, 1.3 gr. daily	Ventricu- lar rate slowed	S.R. in 1 hr.	None	None	None	Dig. leaf, 3 gr. daily	Poor; recur- rence in 2 wk.	Un- stable	Eight recurrences of A. Fl. in 7 mo. fol- lowing primary ther- apy
11 (D. I.)	74	M	None made	A.Fl.; V.R., 160; L. B.B.B.	21 days	Palp.; dysp.; syn- cope	L.H.F.	None	None	1.6 I.V. plus 1 mg. daily	Ventricu- lar rate slowed	A. Fib. in 2 hr., 50 min.	20 gr. daily	None	S.R. in 24 hr.	Lanat. C, 1 mg. daily	Good	8 mo.	None
12 (E. McP.)	75	M	H.Cv. D.	A.Fl.; V.R., 170	8 days	Palp.; dysp.	L.H.F., Diab. mcl. with gang.	None	None	1.6 I.V.	Ventricu- lar rate slowed	S.R. in 1 hr.	None	None	None	Lanat. C, 1 mg. daily	Good	10 days	Patient had supra- condylar amputa- tion for gangrene; expired 10 days later
13 (J. M.)	66	M	H.Cv. D.	A.Fl.; V.R., 150	20 days	Dysp.	C.H.F. (severe)	None	None	1.6 I.V. plus 2 mg. daily	Ventricu- lar rate slowed	2-1 A-V block, in 2 hr.; S.R., in 24 hr.	None	None	None	Lanat. C, 1 mg. daily	Good	12 mo.	Dismissed fully com- pensated 20 days after entry
14 (F. T.)	61	M	Coron. H.D.	A.Fl.; V.R., 150	10 days	Dysp.	C.H.F., edema	None	None	1.6 I.V. plus 2 mg. daily	Ventricu- lar rate slowed	A. Fib., in 24 hr.	24 gr. daily	None	S.R. in 48 hr.	Lanat. C, 1 mg. daily	Good	7 mo.	Patient had previous coronary occlusion and developed C.H. F. after intractable flutter

TABLE I. RESULTS OF THE COMBINED USE OF LANATOSIDE C AND QUINIDINE SULFATE IN THE TREATMENT OF TWENTY-ONE PATIENTS WITH ACHYLLER FLUTTER CONT'D

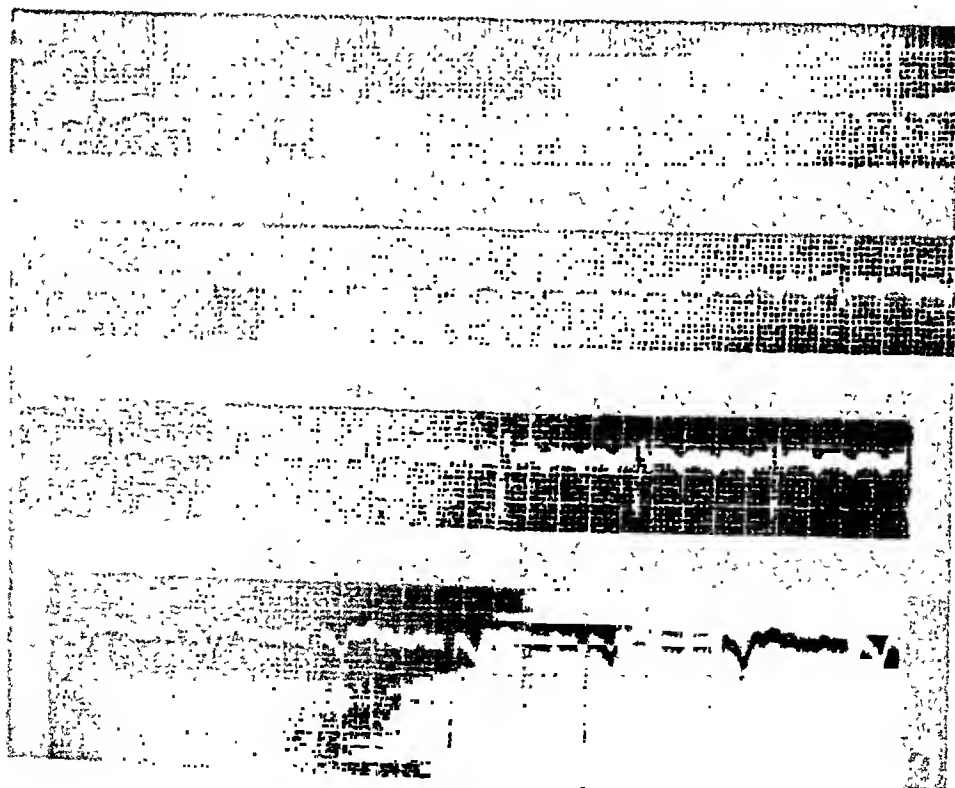
CASE	AGE	SEX	DIAGNOSIS		SYMPTOMS		PREVIOUS MEDICATION	EFFECT OF PREVIOUS MEDICATION	LANATOSIDE C DOSAGE IN MG.	LANATOSIDE C RESULT		ORAL QUINIDINE DOSAGE	QUINIDINE RESULT		FOLLOW-UP THERAPY	RESULT OF THERAPY	DURATION OF S. R.	REMARKS
			CHIN- CAL.	ECG	DURA- TION	SYMP- TOMS	ORI.			IMMED.	LATENT		IMMED.	LATENT				
15 (R. S.)	65	F	H.C.v. D.	A.Fl.; V.R., 160	0 days	Weak; palp.	Tachy.	None	None	1.6 I.V. plus 1 mg. daily	Ventric- ular rate slowed	A. Fib. in 24 hr.	None	S.R. in 72 hr.	Dig. leaf, 1 1/2 gr. daily	Good	4 mo.	None
16 (J. K.)	37	M	H.C.v. D.; Br. Asth.	A.Fl.; V.R., 110	10 days	Dysp.	C.H.F. (Severe)	None	None	1.6 I.V. plus 2 mg. daily	Ventric- ular rate slowed	A. Fib. 13 days later	None	S.R. 10 days later	Lanat. C, 1 mg. daily	Delayed but good	9 mo.	Drug action extremely slow
17 (L. C.)	51	M	None	A.Fl.; V.R., 152	28 days	Dysp.	C.H.F. (Mild)	None	None	1.6 I.V. plus 1 mg. daily	Ventric- ular rate slowed	A. Fib. in 24 hr.	None	S.R. 7 days later	Lanat. C, 2 mg daily	Good	4 mo.	Slow conversion of A. Fib. to S.R.
18 (P. H.)	51	M	Alcohol- ism and Br.Pn	A.Fl.; V.R., 156	25 days	Weak; dysp.; syn- cope	Br. Pn.	Dig. leaf, 31 gr.	None	1.6 I.V. plus 1 1/2 daily	Ventric- ular rate slowed	A. Fib. in 48 hr.	None	S.R. 24 hr later	Lanat. C, 1 mg. daily	Good	6 mo.	None

19 (J. H.)	41	M	None	A.Fl.; V.R., 150	12 days	Weak; dysp.; P. pain	Tachy.	Quinidine, dig. leaf, mecholyt (amount un- known)	None	1.6 I.V. plus 2 mg. daily	Ventric- ular rate slowed	A. Fib. in 12 hr.	24 gr. daily	None	S.R. in 16 hr.	Lanat. C, 1 mg. daily	Good	5 mo.	Many previous at- tacks of A. Fl.
20 (M. S.)	62	M	Art. Scl. H.D.	A.Fl.; V.R., 146	9 days	Palp.; weak; dysp.; P. pain	Tachy., C.H.F. (mild)	None	None	1.6 I.V. plus 1.5 daily	Ventric- ular rate slowed	A. Fib. in 24 hr.	36 gr. daily	None	S.R. in 36 hr.	Lanat. C, 1 mg. daily	Good	2 mo.	Expired of myocardial infarct. approx. 60 days after S.R. was established
21 (J. K.)	65	M	Art. Scl. H.D.	A.Fl.; V.R., 160	14 days	Weak; palp.; dysp.	Coron. anoxia	None	None	1.6 I.V. plus 2 mg. daily	Nodal tachy. V. es.	A. Fib. in 6 hr.	20 gr. daily	None	S.R. in 2 hr. follow- ed by nodal tachy- 6 hr. later	Mech- olyl, 0.35 Gm.	Poor	2 hr.	Expired of myocardial infarct. involving septum

A. Fl., Auricular flutter; A. Fib., auricular fibrillation; S. R., sinus rhythm; V. R., ventricular rate; V. P. C., ventricular premature contraction; L. B. B. B., left bundle branch block; C. H. F., congestive heart failure; L. H. F., left heart failure; R. H. D., rheumatic heart disease; H. C. V. D., hypertensive cardiovascular disease; I. V., intravenously; Br. Ph., bronchopneumonia; C. V. A., cardiovascular accident; P. pain, precordial pain; V. es., ventricular extrasystoles.

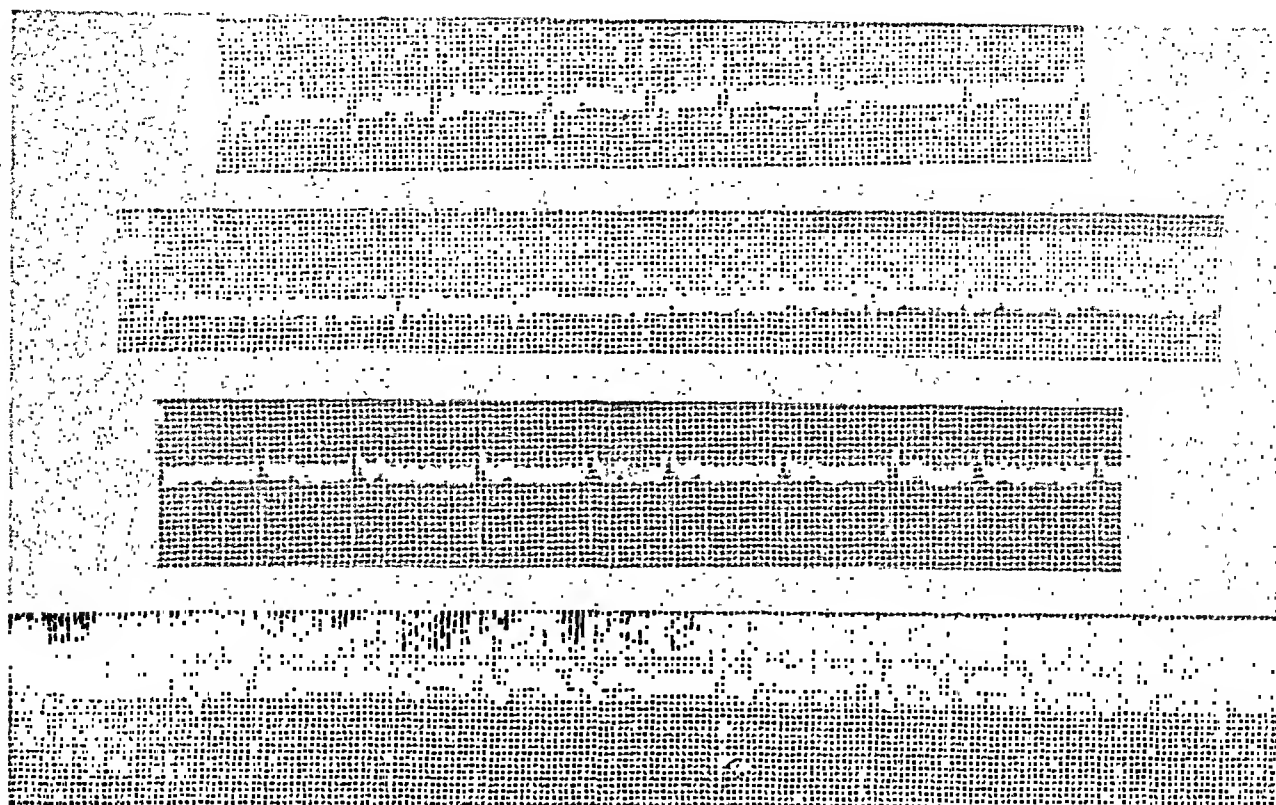


A.

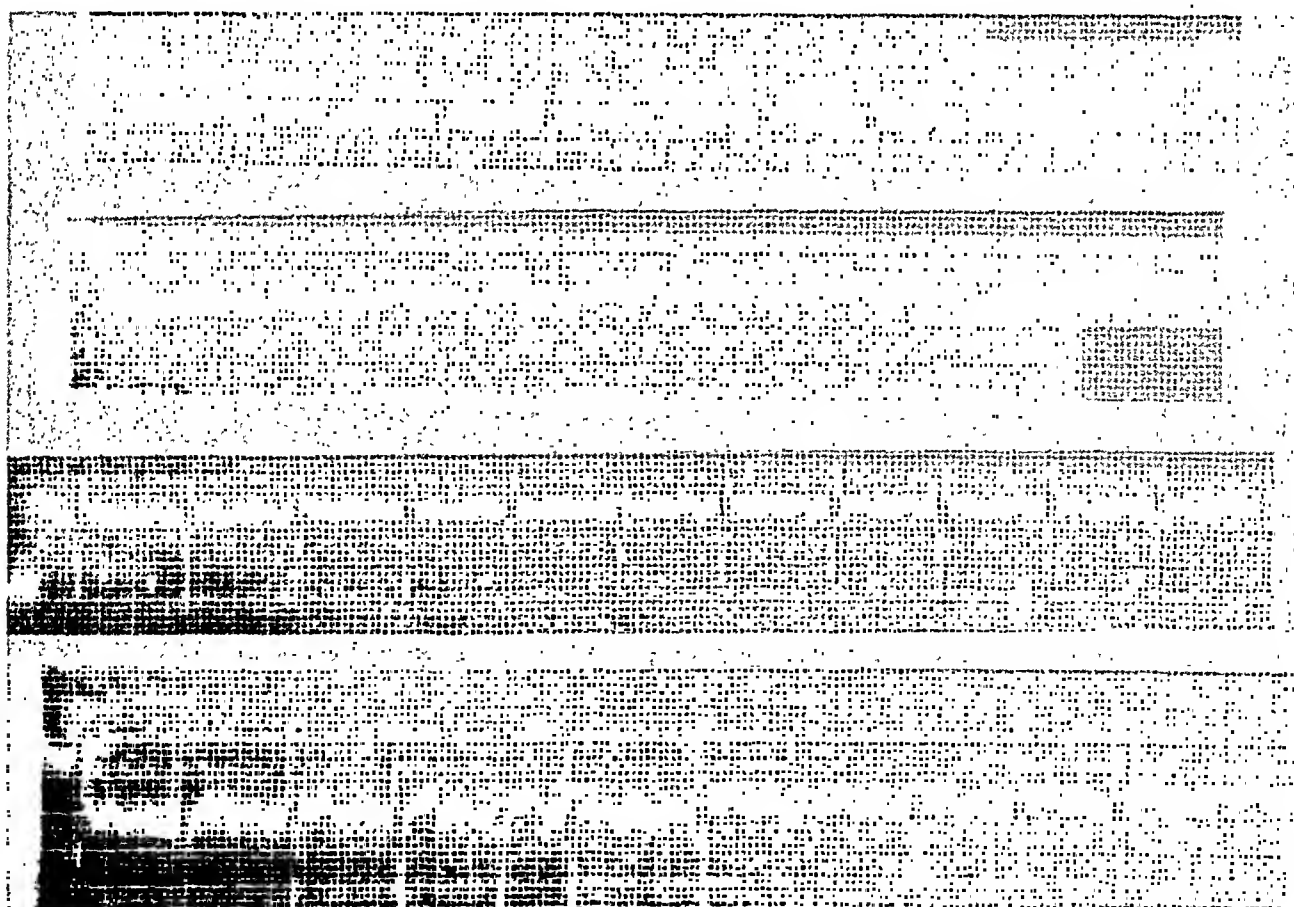


B.

FIG. 1.—Case 3. Conversion of auricular flutter in the presence of associated disease. A, Auricular flutter with 2 to 1 A-V block. Ventricular rate, 140 per minute. B, Increased A-V block four hours following 1.6 mg. of lanatoside C intravenously. C, Demonstrating auricular fibrillation seventy-two hours after initial dosage of lanatoside. D, Restoration of sinus rhythm twenty-four hours after withdrawal of lanatoside. Total dosage, 24 grains.

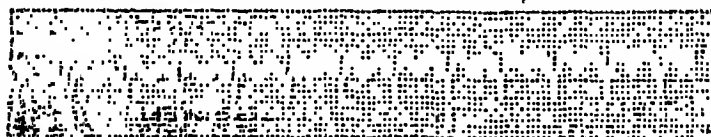
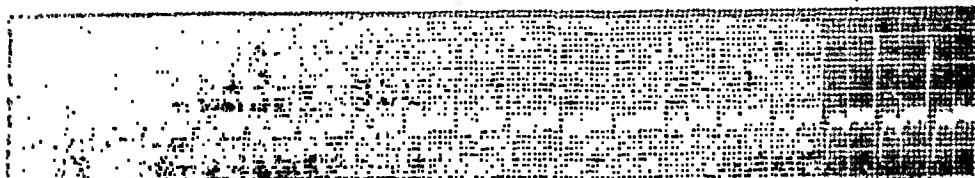
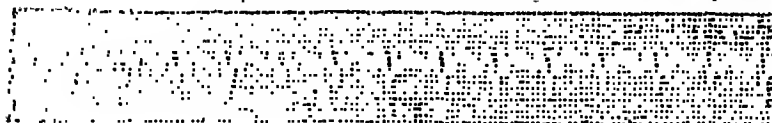
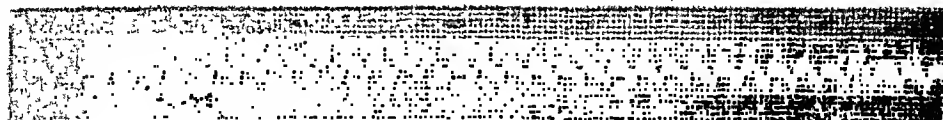
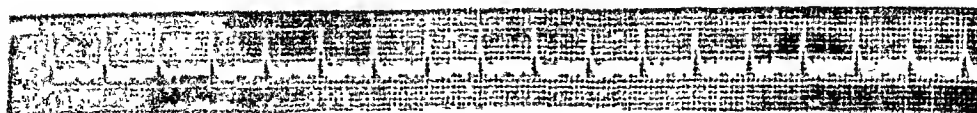


C.

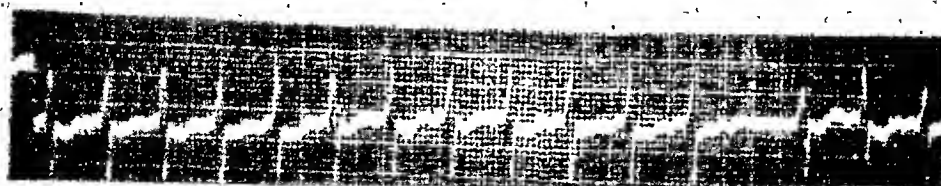
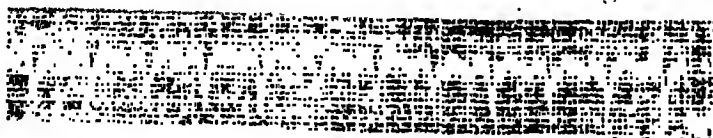
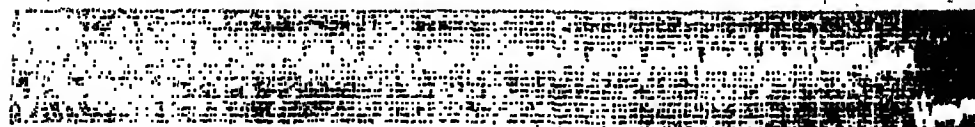
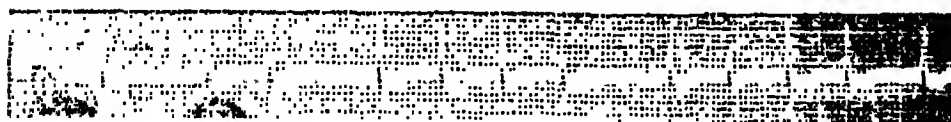


D.

Fig. 1 (Cont'd).—For complete legend, see opposite page.

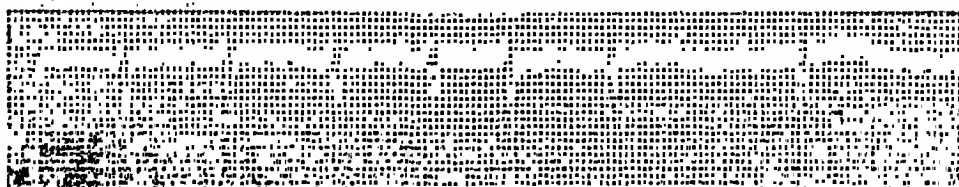
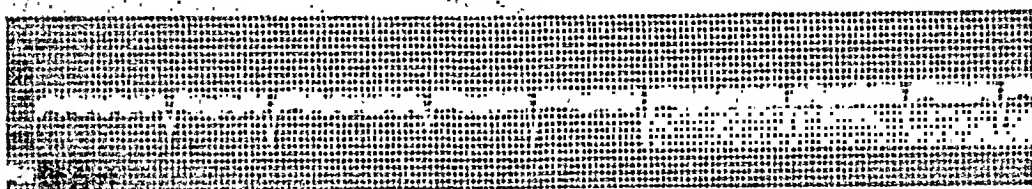
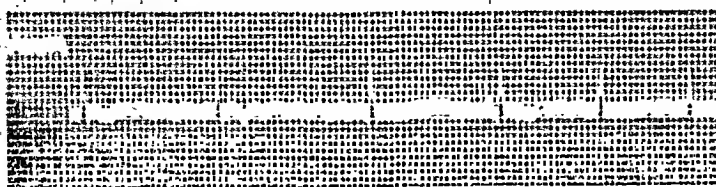
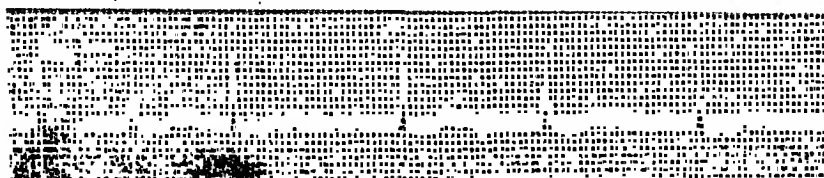


A.

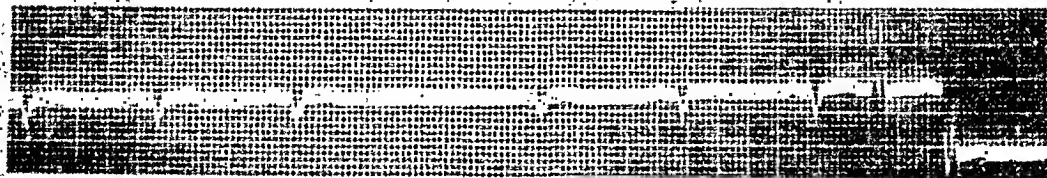
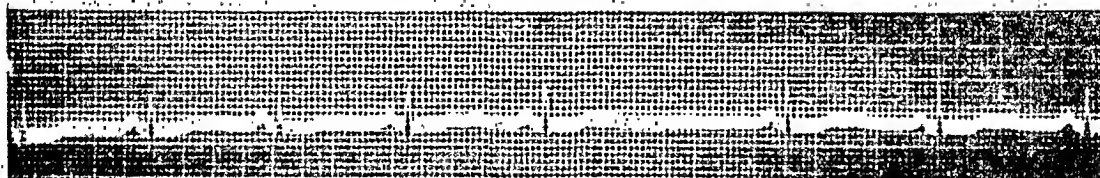
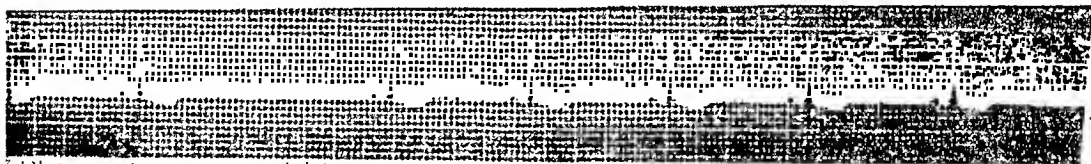


B.

FIG. 2.—Case 19. Conversion of auricular flutter by lanatoside C and quinidine. A, Auricular flutter with 2 to 1 A-V block. Ventricular rate, 150 per minute. B, Thirty minutes after 1.6 mg. of lanatoside C intravenously. Note slowing effect with increased A-V block. C, Conversion to auricular fibrillation twelve hours after initial dosage of lanatoside C. D, Restoration of sinus rhythm sixteen hours after administration of 24 gr. of quinidine. E, Tracing twenty-four hours after conversion to sinus rhythm. Patient receiving 1 mg. of lanatoside C daily. Voltage has increased and slight left ventricular strain has made its appearance.



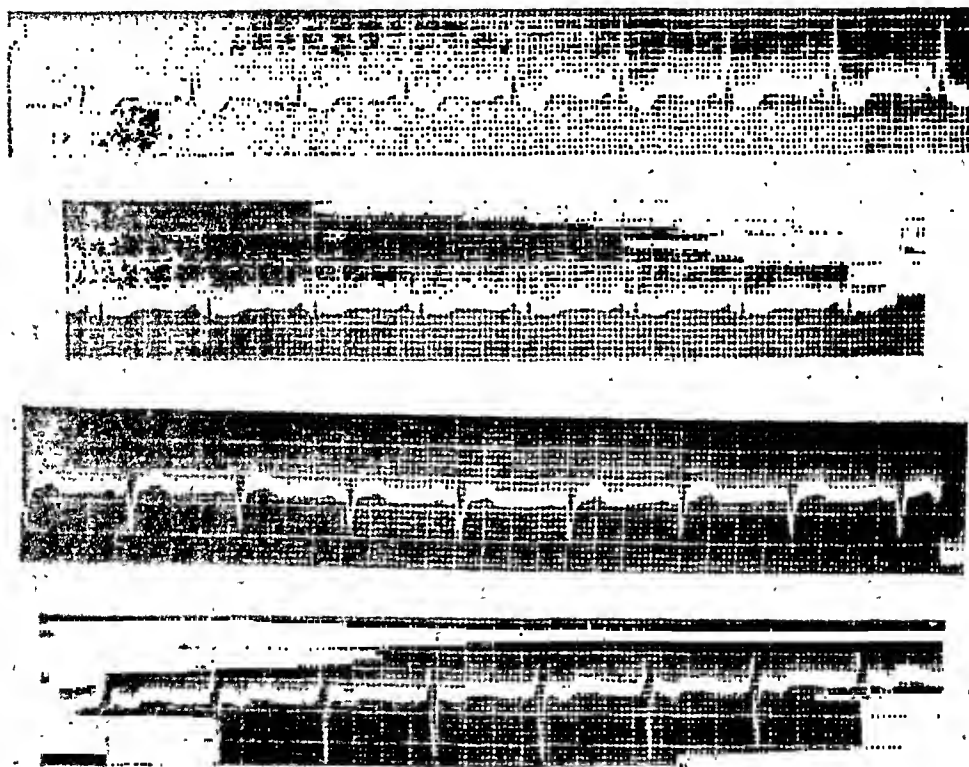
C.



D.

Fig. 2 (Cont'd).—For complete legend, see opposite page.

Quinidine sulfate was given orally to fifteen of those in whom auricular flutter was converted into auricular fibrillation. In addition, a maintenance dosage of lanatoside C, consisting of 1 mg. daily, was given. One patient was intolerant to quinidine and the drug had to be discontinued. In the remaining fourteen patients of this group, auricular fibrillation was successfully converted to sinus rhythm over a period of from twelve hours to ten days. The dosage of quinidine was based on individual tolerance and clinical results, and varied from 0.7 to 1.44 Gm. in twenty-four hours. In one patient the auricular flutter recurred immediately after the quinidine was discontinued. This patient had chronic rheumatic heart disease with a history of multiple attacks of auricular paroxysmal tachycardia and auricular flutter since childhood. In another, sinus rhythm was followed by nodal tachycardia and sudden death. Autopsy revealed the presence of an extensive myocardial infarct involving the interventricular septum and a portion of the interauricular septum.



E.

Fig. 2 (Cont'd).—For complete legend, see page 626.

The entire group of patients with successfully restored sinus rhythm received a maintenance dosage of lanatoside C and were observed for a period of from two to thirty-four months following the institution of this study. The average time of observation was eleven months. So far as we have been able to determine, there has not been a single recurrence of auricular flutter. As a rule the successfully treated members of this group were discharged from the hospital within one week after the restoration of normal rhythm.

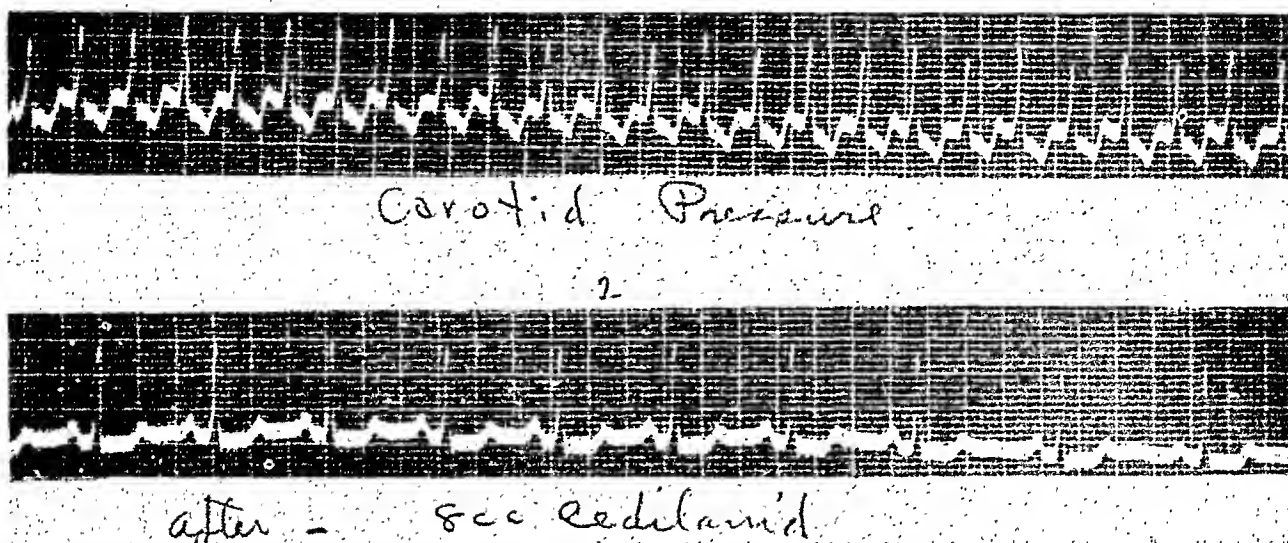


Fig. 3.—Case 2. Direct conversion of auricular flutter to sinus rhythm. Note: Carotid pressure was ineffectual. Sinus rhythm obtained in 50 minutes following 1.6 mg. of lanatoside C intravenously. Tracing taken in Lead II.

DISCUSSION

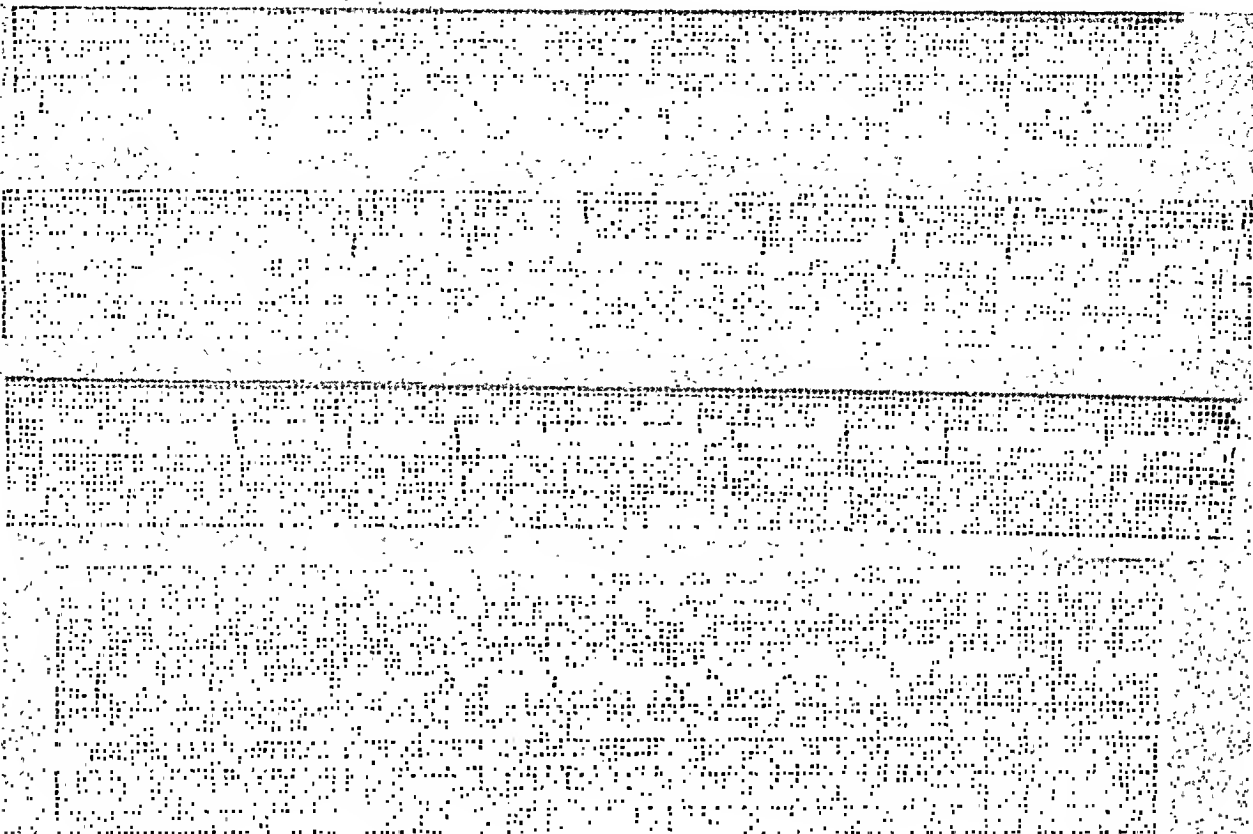
On the basis of historical and clinical evidence, we feel justified in classifying the auricular flutter in this group of patients as established. Many of the patients had failed to respond to varied therapeutic procedures, including quinidine and digitalis leaf alone and in combination. After reviewing the literature and considering our own experience, we feel that quinidine has no place in the initial therapy of auricular flutter. There are sound pharmacologic reasons for its failure. Digitalis, on the other hand, may be initially effective in the conversion of this arrhythmia to sinus rhythm or auricular fibrillation, especially if it be given intravenously in full dosage as the glycoside lanatoside C. Digitalis leaf frequently fails to convert this arrhythmia, and, when it does, this conversion is invariably very slow in occurring. Lanatoside C, due to its rapidity of action and strong vagal effect, has been shown to possess superiority over digitalis leaf in the treatment of established auricular flutter. This action is further fortified by follow-up maintenance therapy with the same drug. In patients whose auricular flutter was successfully converted to auricular fibrillation, the time for the conversion varied from two to seventy-two hours; in one patient the conversion did not occur until thirteen days after the initial medication. Serial electrocardiograms made at frequent intervals during the transition from auricular flutter to auricular fibrillation were exceedingly valuable therapeutic guides. We found that adequate medication should be maintained until conversion is complete. Utmost patience should be combined with careful clinical observation throughout the conversion period, particularly when complicating disease is present, as it was in four patients of our series. The presence of associated disease unquestionably prolonged the conversion period.

Little attention has been given to the primary slowing of the ventricular rate which occurs when lanatoside C and other forms of digitalis are given in auricular flutter. This slowing effect designates an increase in A-V block, and

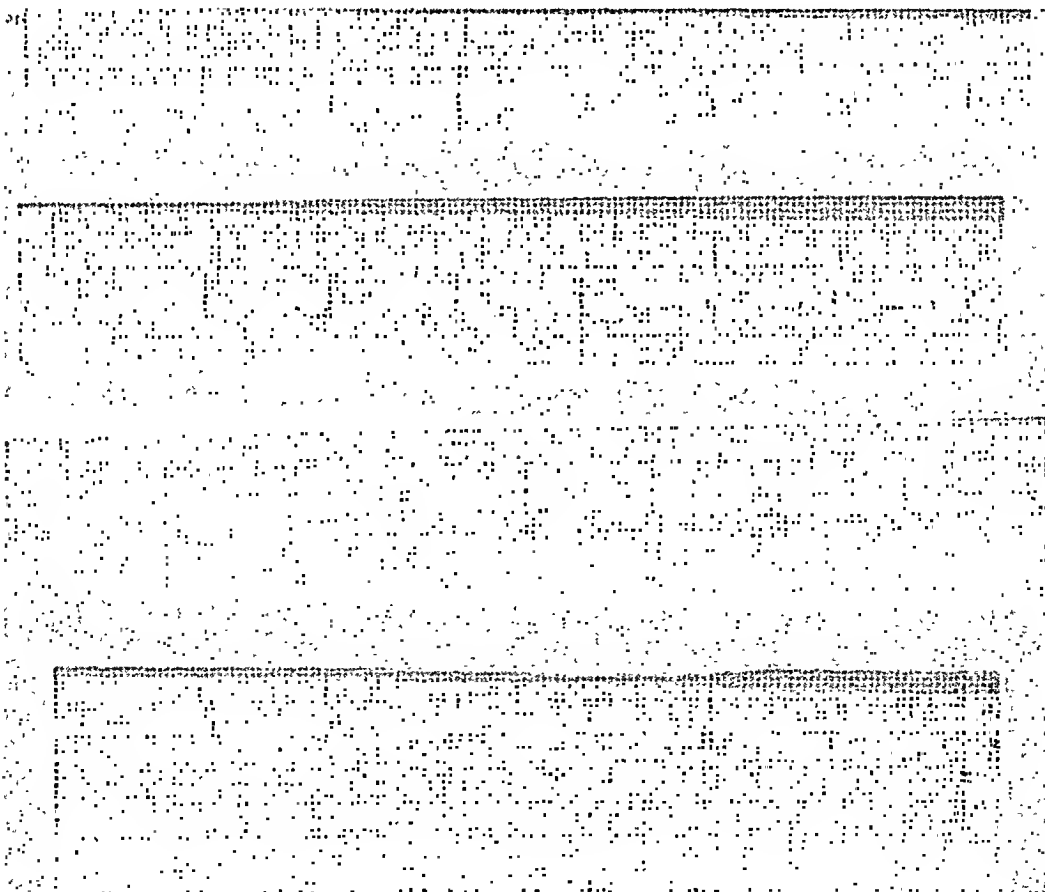
A.

B.

Fig. 4.--For complete legend, see opposite page.



C.



D.

Fig. 4.—Case 13. Direct conversion of auricular flutter to sinus rhythm with 1.6 mg. of lanatoside C intravenously. A, Auricular flutter with a ventricular rate of 150 per minute. B, Two hours later demonstrating slowing effect and increased A-V block. C, Twenty-four hours after lanatoside C establishment of sinus rhythm. Note: Occasional auricular premature contractions were present. D, Three days later. Patient receiving 1 mg. lanatoside C daily.

this block usually precedes the appearance of auricular fibrillation. We wish to emphasize the necessity of continued lanatoside C therapy in maintenance dosage until auricular fibrillation makes its appearance.

It is difficult to explain the mechanism of the direct conversion of auricular flutter into a sinus rhythm. This occurred in four of our patients. We feel that conversion might have occurred spontaneously in due time without the aid of medication.

The effect of quinidine in the presence of auricular fibrillation is well known; this drug is given according to individual requirements, satisfactory clinical effectiveness can be expected. In this study the time necessary for the conversion of auricular fibrillation into sinus rhythm by the use of quinidine varied from twelve hours to ten days.

When sustained auricular flutter requires both lanatoside C and quinidine in sequence to produce sinus rhythm, it seems plausible to assume that the conversion would not have occurred spontaneously. The use of these drugs, therefore, appears to be of value in the treatment of auricular flutter.

SUMMARY AND CONCLUSIONS

1. Lanatoside C and quinidine sulfate used in proper sequence are valuable drugs for the conversion of established auricular flutter into normal sinus rhythm.
2. Lanatoside C in full digitalizing dosage (1.6 mg.) followed by maintenance dosage (1 to 2 mg. daily) frequently converts auricular flutter to auricular fibrillation, and less frequently to sinus rhythm.
3. Following the administration of this drug, a primary slowing of the ventricular rate occurs which, in the main, is due to increased A-V block. This slowing usually precedes the conversion of auricular flutter to auricular fibrillation.
4. Except in the direct conversion of auricular flutter to sinus rhythm, the action of lanatoside C can be readily understood.
5. The action of quinidine in the presence of auricular fibrillation is quite dependable and well known.
6. Following the conversion of auricular flutter to auricular fibrillation by lanatoside C, the use of quinidine has proved of especial value in this study.
7. Conversion of established auricular flutter to sinus rhythm can be accomplished in the presence of diversified pathology.
8. Maintenance dosage of lanatoside C has proved of value as prophylactic therapy following the restoration of normal sinus rhythm.

REFERENCES

1. White, P. D.: *Heart Disease*, ed. 3, New York, 1944, The Macmillan Co., p. 907.
2. Lewis, T., Drury, A. N., Hie-cu, C. C., and Wedd, A. M.: Observations Relating to the Action of Quinidine Upon the Dog's Heart; With Special Reference to Its Action in Clinical Fibrillation of the Auricles, *Heart* 9: 55, 1921.
3. Parkinson, J., and Bedford, D. E.: The Course and Treatment of Auricular Flutter, *Quart. J. Med.* 21: 21, 1927.

4. Lewis, T., and Drury, A. N.: Revised Views of the Refractory Period, in Relation to Drugs Reputed to Prolong It, and in Relation to Circus Movement, *Heart* 13: 95, 1926.
5. Wedd, A. M.: Notes on the Action of Certain Drugs in Clinical Flutter, *Heart* 11: 87, 1924.
6. Wilson, F. N., and Wishart, S. W.: The Effect of the Intravenous Administration of Digitalis in Paroxysmal Tachycardia of Supraventricular Origin, *AM. HEART J.* 5: 549, 1930.
7. Tandowsky, R. M.: An Electrocardiographic and Clinical Study of Lanatoside C, *AM. HEART J.* 24: 472, 1942.
8. Lewis, T., Drury, A. N., and Iliescu, C. C.: Some Observations Upon Atropine and Strophanthin, *Heart* 9: 21, 1921.
9. Barker, P. S., Wilson, F. N., and Johnston, F. D.: The Mechanism of Auricular Paroxysmal Tachycardia, *AM. HEART J.* 26: 435, 1943.
10. Author's observations during the past five years.
11. Ray T., and LaDue, J. S.: The Intravenous Administration of Lanatoside C to Patients Taking Maintenance Doses of Folia Digitalis Up to the Date of Hospitalization With Recurrent Congestive Heart Failure, *AM. HEART J.* 30: 335, 1945.
12. Tandowsky, R. M., Anderson, N., and Vandeventer, J. K.: An Electrocardiographic and Clinical Study of Various So-Called Cardiac Drugs, *AM. HEART J.* 28: 298, 1944.
13. Tandowsky, R. M.: Prophylactic Use of Lanatoside C in Auricular Paroxysmal Arrhythmias, *AM. HEART J.* 29: 71, 1945.

ELECTROCARDIOGRAPHIC CHANGES OCCURRING DURING TREATMENT WITH FUADIN SOLUTION

S. B. BEASER, M.D.,* AND R. RODRIGUEZ-MOLINA, M.D.†

CLINICAL medicine recognizes heart disease as one of the commonest causes for sudden death. In any condition, therefore, in which sudden death occurs, a cardiac origin should be suspected; moreover, evidence for unsuspected cardiac dysfunction in nonfatal cases of that disorder should be sought for. One such disorder is the toxicity due to antimony therapy of schistosomiasis.¹⁻³ Manzer and Krause,¹ after observing such a fatality, performed electrocardiograms routinely on twelve patients receiving intravenous tartar emetic and found abnormalities in eight of them, all of whom were asymptomatic. The accidental finding of similar electrocardiographic changes in a patient receiving the reputedly less toxic fuadin (sodium antimony pyrocatechin) led to the present systematic electrocardiographic study of twenty-five patients under treatment for schistosomiasis with that drug.

PLAN OF STUDY

All twenty-five patients were Puerto Rican soldiers with schistosomiasis (Mansoni) who were receiving a uniform course of fuadin therapy. Electrocardiograms‡ were taken before and during treatment (Table I). The usual limb leads and CF₄ were taken with the patient in the same position and with standardizations recorded no sooner than two and one-half hours after meals⁴ and one hour after the fuadin injections. Additional electrocardiograms were taken just after the tenth injection on certain positive cases as follows: two in inspiration and expiration both in the recumbent and upright positions; one fifteen minutes after the intravenous injection of 1/50 gr. of atropine dissolved in 10 c.c. of distilled water; one with bilateral carotid sinus pressure. In fourteen of the twenty patients who showed electrocardiographic changes, twenty-two follow-up electrocardiograms were performed during the three weeks after cessation of therapy.

The tracings were analyzed for all the common factors. The P-R interval was used as the basis for the isoelectric line and five successive complexes were averaged for each measurement. Following the criteria of Larsen and co-workers,⁵ the outer limit of normal variation of the amplitude of T waves was con-

Received for publication April 20, 1946

*Assistant in Medicine, Harvard Medical School, and Head of The Diabetic Clinic, Beth Israel Hospital, Boston, Mass. (on leave of absence in the United States Army).

†Assistant Professor of Tropical Medicine, School of Tropical Medicine, San Juan, Puerto Rico, and Columbia University, New York, N. Y. (on leave of absence in the United States Army)

‡The General Electric Electrocardiograph (Model B) was used throughout.

TABLE I. FUADIN* THERAPY (DOSAGE SCHEDULE)

Day of treatment	0	1	2	3	5	7	9	11	13	15	17
Number of fuadin injections	0	1	2	3	4	5	6	7	8	9	10
Dose of fuadin in cubic centimeters	0	1.5	3.5	5	5	5	5	5	5	5	5
Accumulated dose of fuadin In cubic centimeters	0	1.5	5	10	15	20	25	30	35	40	45
In milligrams	0			0.63				1.89			2.84
Accumulated dose of antimony in milligrams	0			0.085				0.255			0.383
ECG performed	Control ECG			ECG				ECG			ECG

*Each cubic centimeter of fuadin solution contains 0.063 Gm. of fuadin and 0.0085 mg. of trivalent antimony.

sidered to be 0.1 mv, and definite changes had to persist for at least two tracings in order to be regarded as significant. Certain cases were considered to show no change, even though the T waves had a definite tendency to decrease in voltage (six in all), since they did not conform to the foregoing criteria. The ventricular gradient was measured* in one instance (Leads I and II of A and D of Fig. 2) according to the method of Wilson and co-workers.⁶

RESULTS

Significant changes from the normal were noted only in the T waves and S-T segments (Table II and Figs. 1-6). The analysis which included all important elements of the tracings showed no significant QRS, Q-T, or rate changes. Of the total of twenty-five patients, twenty, or 80 per cent, showed significant decrease in the height of the T waves in two or more leads. The amplitude of the T waves decreased therefore in fifty-nine of a total of 100 T waves. Seven patients developed T-wave changes in all four leads. In two (Figs. 2 and 4), T₄ had a cove-plane configuration.¹⁶ The regression of the abnormal changes of forty-one T waves in fourteen patients was studied in detail in terms of the percentile return toward the pretreatment normal value of each T wave in the three weeks following cessation of treatment (Table III). These values can be considered only as estimates of the speed of recovery. Changes in position, inspiration and expiration, atropine, and carotid sinus pressure did not significantly alter the T-wave changes noted previously. The ventricular gradient showed a counterclockwise rotation to the left and a decrease in magnitude (Table IV and Fig. 7).

*We are indebted to Dr. A. Stone Freedberg for this analysis.

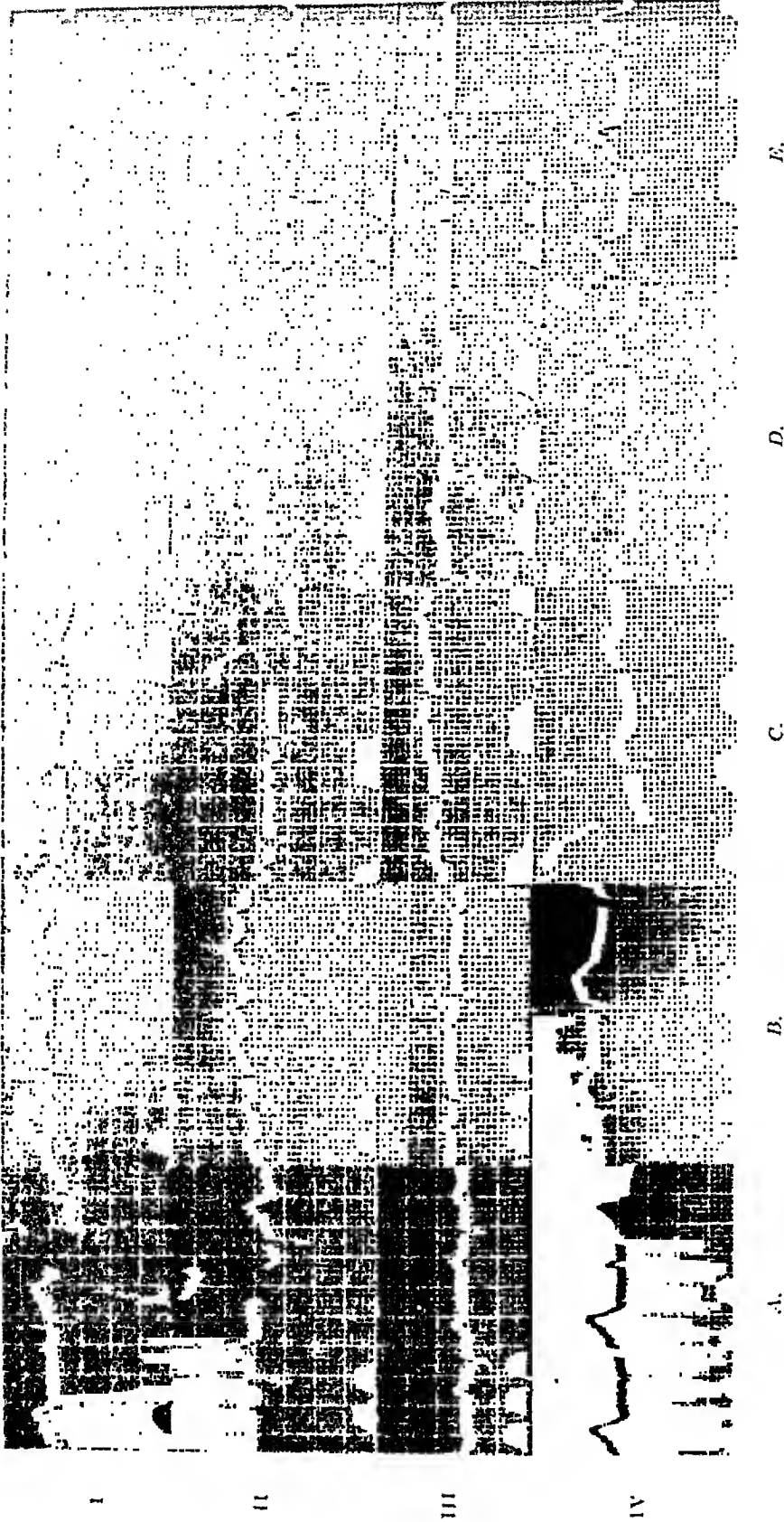


Fig. 1.—Case 1. A, Control; B and C, injections 7 and 10, respectively; D and E, four and eleven days, respectively, after C.

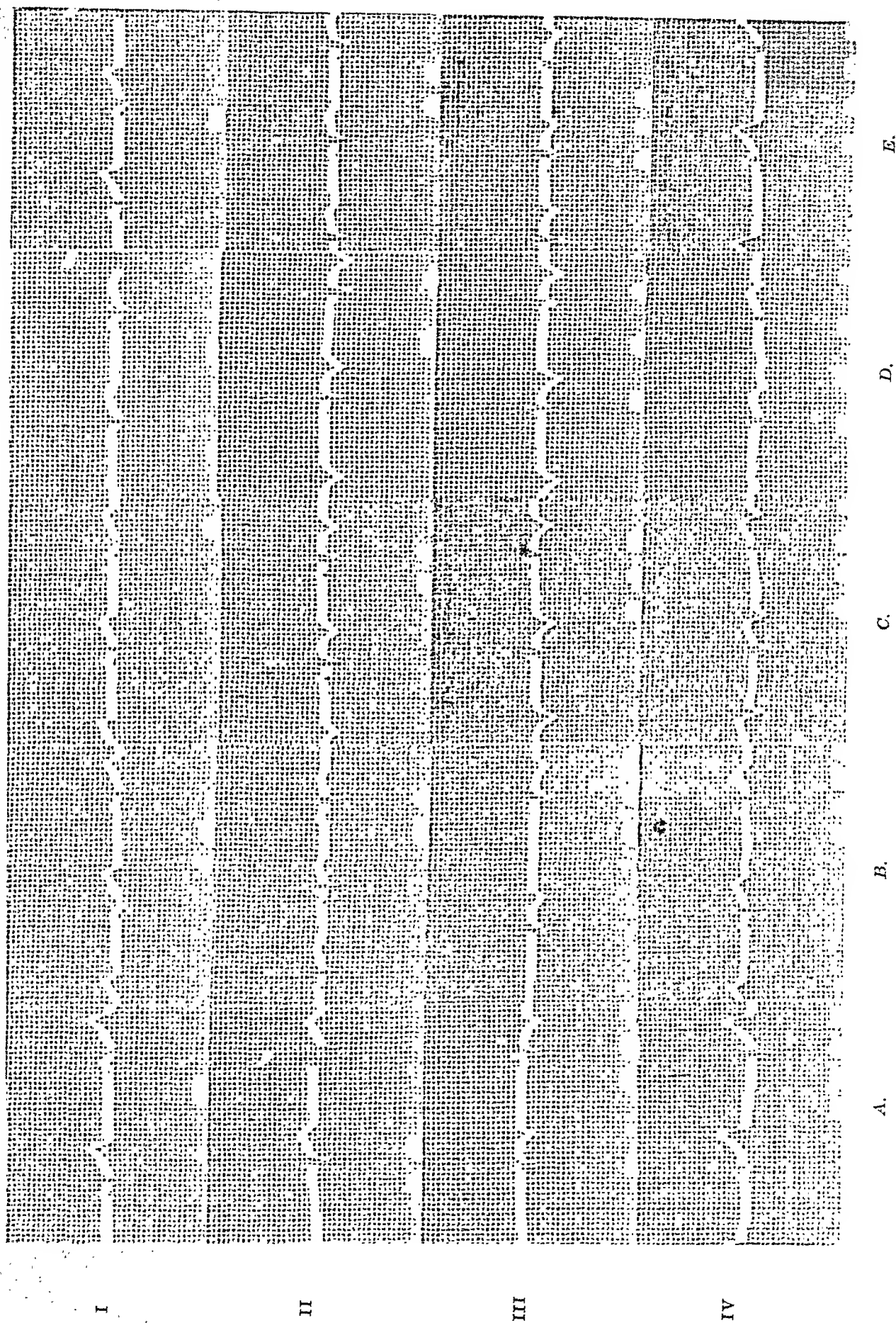
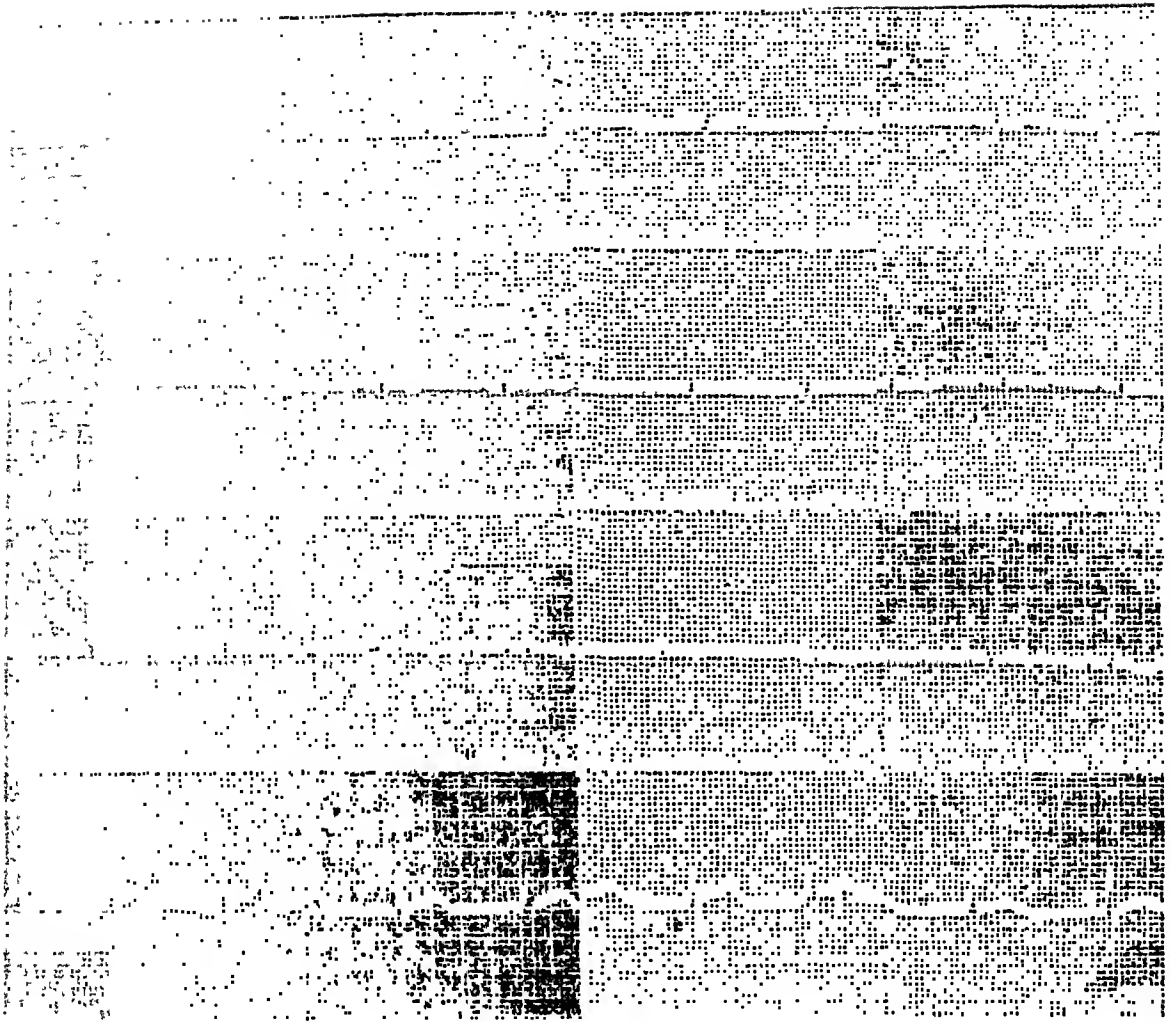


Fig. 2.—Case 5. A, Control; B, C, and D, injections 3, 7, and 10, respectively; E, seventeen days after D.



A. B. C. D.

Fig. 3.—Case 6. A, Control; B and C, injections 7 and 10, respectively; D, three days after C.

TABLE II. ANALYSIS OF THE T-WAVE CHANGES OCCURRING DURING FUADIN THERAPY

	NUMBER OF PATIENTS DEVELOPING T-WAVE CHANGES	NUMBER OF PATIENTS DEVELOPING T-WAVE CHANGES AT INJECTION NUMBER			NUMBER OF PATIENTS WITH MAXIMUM CHANGE AT INJECTION NUMBER		
		3	7	10	3	7	10
T ₁	14	6	5	3	1	2	11
T ₂	19	14	5	0	0	2	17
T ₃	8	1	4	3	1	2	5
T ₄	18	14	2	2	3	4	12
Total Number Per cent	59 100	35 60	16 27	8 13	4 7	10 17	45 76

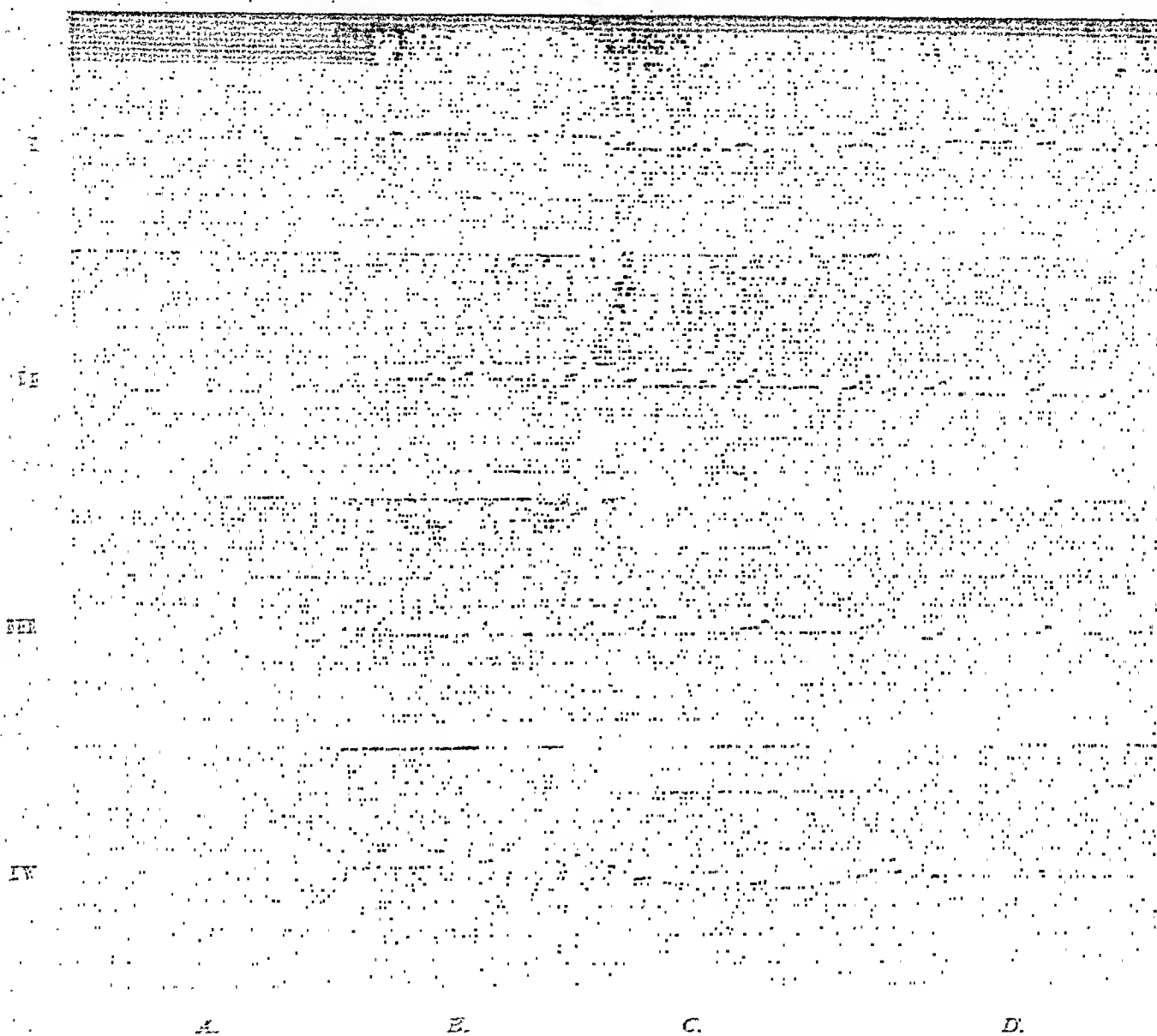


FIG. 4.—Case 17. A, Control; B, C, and D, injections 2, 7, and 10, respectively.

TABLE III. REGRESSION OF T-WAVE CHANGES AFTER CESSATION OF FUADIN THERAPY

	NUMBER OF DAYS AFTER LAST INJECTION		
	0 to 7	8 to 15	16 to 22
Total number cases studied	11	8	3
Average return to normal height of T waves in per cent	33	63	73

TABLE IV. MEASUREMENT OF VENTRICULAR GRADIENT OF CASE 5 (FIG. 2)

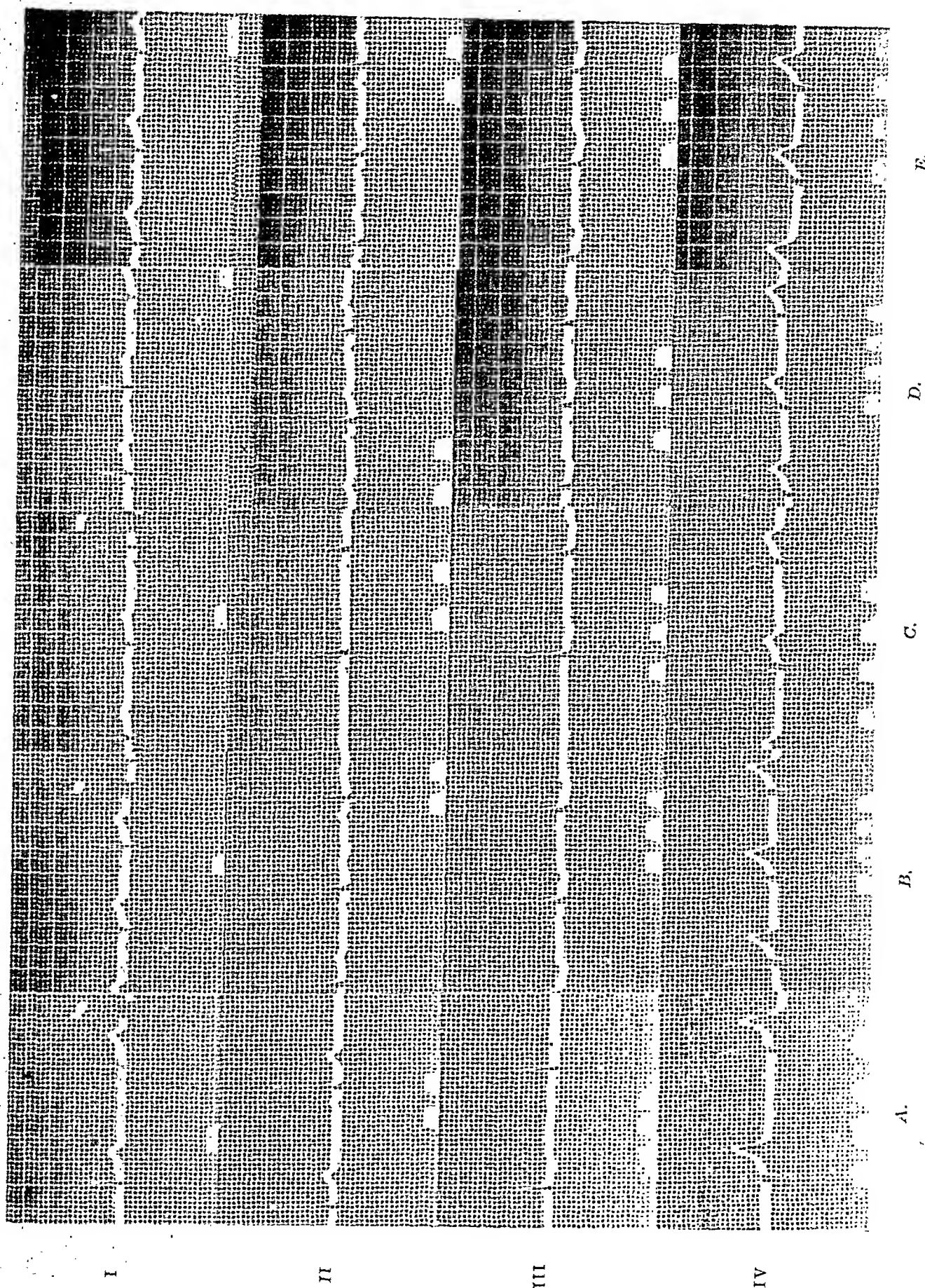
FACTOR	CONTROL (A)	AFTER FUADIN (D)
QRS ₁	+34.0 m. v. s.	+23.5 m. v. s.
I ₁	+59.0 m. v. s.	+16.0 m. v. s.
QRS ₂	+17.0 m. v. s.	+16.0 m. v. s.
I ₂	+31.0 m. v. s.	-28.0 m. v. s.
ΔQRS	35.5 m. v. s.	24.0 m. v. s.
	-1°	+13°
ΔT	59.0 m. v. s.	46.0 m. v. s.
	+1°	-68°
ΔQRS _T	95.0 m. v. s.	54 m. v. s.
	0°	-44°

DISCUSSION

Antimony has been shown to have no immediate effect upon the electrocardiogram of the dog⁹ but does cause weakening of the heartbeat with cardiac dilatation both in dogs⁹ and frogs.^{10,11} In more prolonged toxicity experiments in dogs, this drug has been shown to accumulate chemically much less in the heart than in the lungs, liver, and kidneys.^{12,13} Likewise, pathologic changes in the liver and kidneys preceded heart involvement in the dog. Severe symptoms of hepatic and renal damage were evident at a time when the contrastingly mild heart damage was clinically not evident (electrocardiograms were not taken in these experiments).

In man, the toxic symptoms after antimony treatment consist of vomiting, collapse, fever, and muscular pains. These occur in only 1 per cent of patients receiving fuadin (less than after tartar emetic). The reasons for the variation in individual susceptibility are unknown, but the excretion of fuadin has been noted to vary from person to person, with a noticeable delay in those with renal excretory difficulty. Mainzer and Krause,¹ in their electrocardiographic study of patients under tartar emetic therapy, noted that the heart rate decreased slightly,* that the T waves became flat or inverted, and that the S-T and T elements became "indistinctly separated and fused with one another." They found that the changes occurred early (usually in the second tracing) after 0.72 to 1.08 Gm. of tartar emetic, but they did not determine the recovery rate by following their cases. Magalhães and Dias¹⁵ found similar T-wave changes in twenty-one patients receiving antimony therapy. These changes were present in seven of fourteen of their recorded electrocardiograms. Of these, one-half the patients had received tartar emetic, but it was not clear which antimony compounds the remaining patients had received. After completion of these studies, Tarr¹⁶ published a preliminary report showing that twelve of thirty-eight patients receiving intravenous tartar emetic and two of twenty-eight patients receiving intramuscular fuadin showed significant electrocardiographic changes consisting of decrease in the voltage of the T waves.

*The bradycardia has been shown to be a vagus effect.



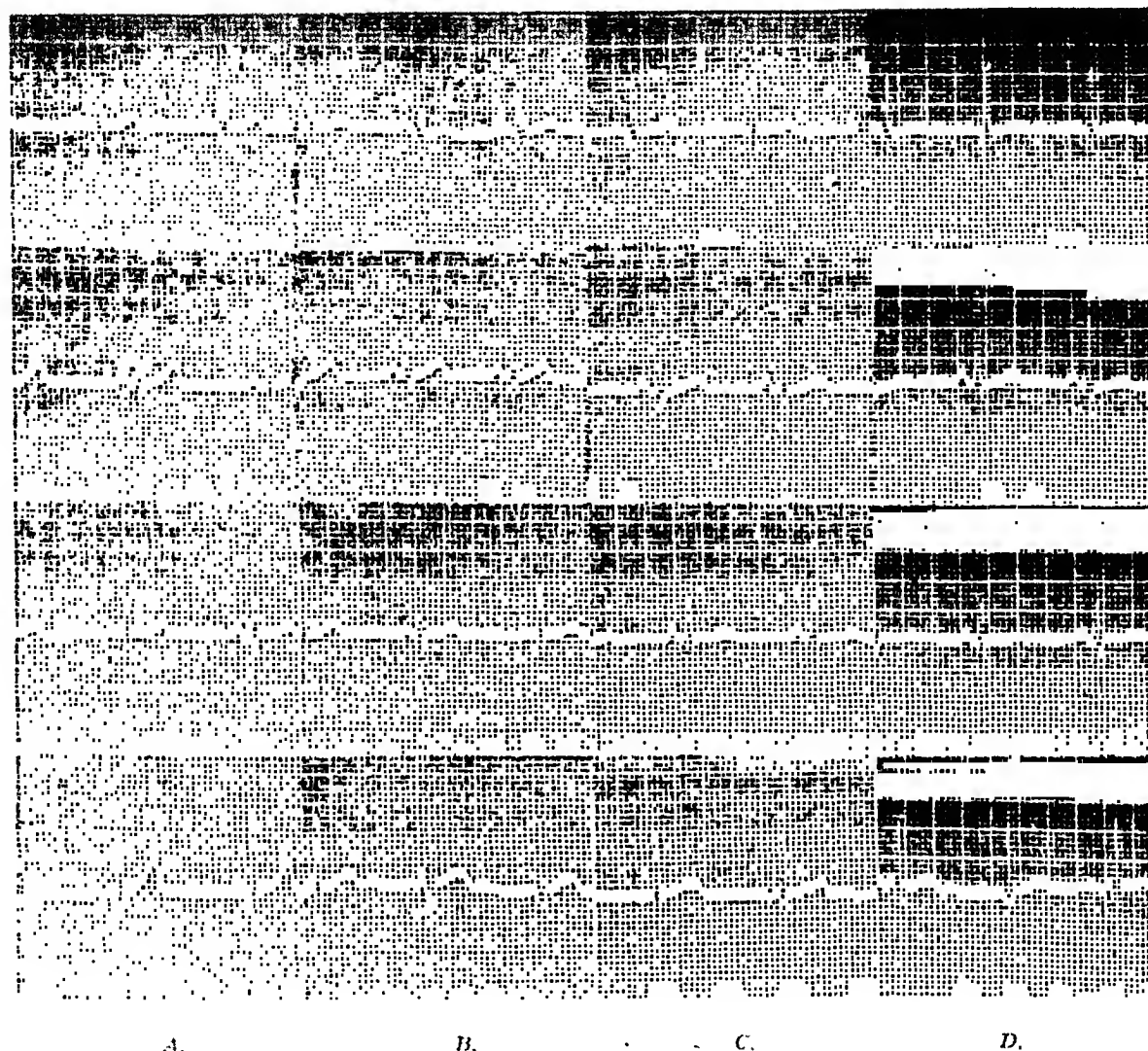


Fig. 6.—Case 25. A, Control; B and C, injections 3 and 10, respectively; D, seven days after C.

The mechanism of the fuadin effect is unknown, but it seems to be definitely reversible. Digitalis, which also has a reversible action upon the myocardium, affects chiefly the magnitude of the ventricular gradient (decrease). A shift in direction of the ventricular gradient has also been noted in myocardial ischemia.¹⁷ This is of interest since Magalhães and Dias¹⁵ ascribed the effects of antimony "to dilatation of the capillaries or the coronary circulation with diminution in the effective circulation to the heart."

Of more than theoretical interest is the similarity of the changes seen after administration of fuadin and those observed in patients with intercurrent infection¹⁸ or phosphorus poisoning¹³ who have been shown to develop similar unsuspected and asymptomatic T-wave changes and who may die suddenly with pathologically demonstrated myocardial changes. Practically, the facts warrant

the clinical precaution that the frequently repeated courses of fuadin be spaced four or more weeks apart to avoid a cumulative effect upon the myocardium, even though that effect is probably reversible in nature.

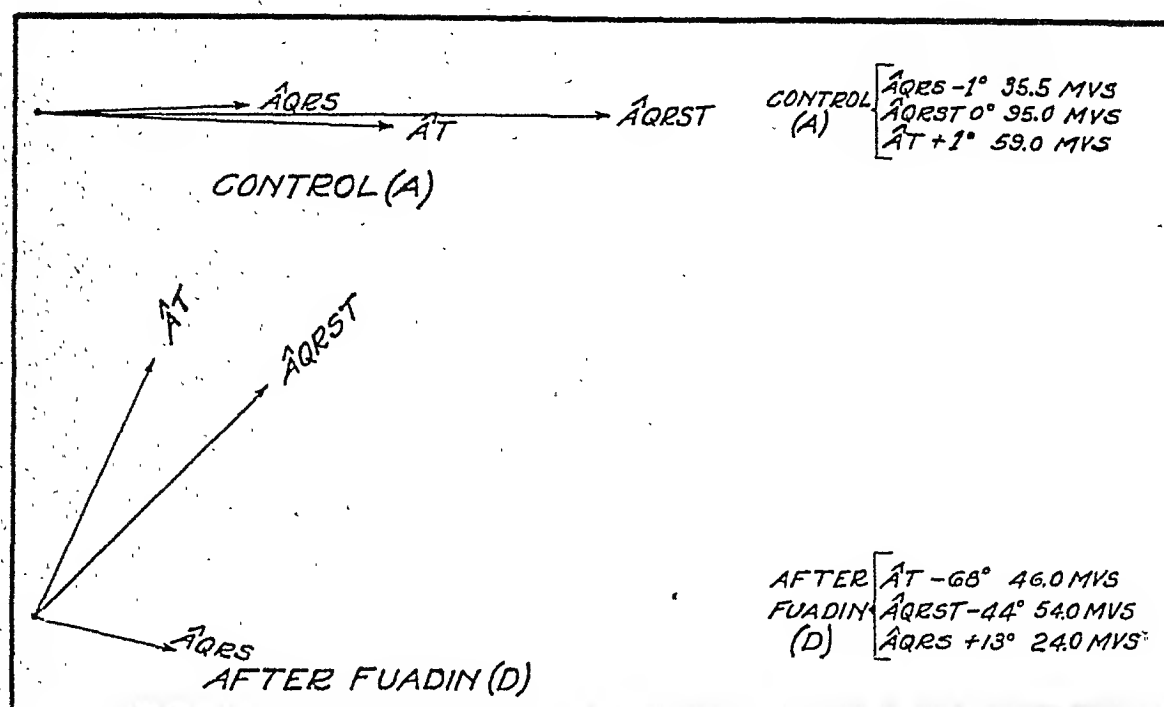


Fig. 7.—Case 5. Ventricular gradient before and after fuadin (Fig. 2, A and D, respectively).

SUMMARY

1. Of twenty-five patients receiving a course of fuadin therapy for schistosomiasis, twenty showed decrease in voltage of the T waves of the electrocardiogram.
2. These changes occurred early (60 per cent after the third injection) and were reversible, regressing in three or more weeks.
3. The ventricular gradient in one patient was analyzed and showed a definite shift in direction.

REFERENCES

1. Mainzer, F., and Krause, M.: Changes of the Electrocardiogram Appearing During Antimony Treatment, Tr. Roy. Soc. Trop. Med. & Hyg. 33: 405, 1940.
2. Khalil, M. B.: The Specific Treatment of Human Schistosomiasis (Bilharziasis) With Special Reference to its Application on a Large Scale, Arch. f. Schiffs- u. Tropen-Hyg. 35: 1, 1931.
3. Khalil, M. B.: Individual Variation in the Excretion of Drugs as an Important Factor in Their Therapeutic Results. A Practical Method for Detecting the Schistosomiasis Cases With So-Called Idiosyncrasy to Antimony to Avoid Fatalities and Complication, J. Egyptian M. A. 19: 285, 1936.
4. Gardberg, M., and Olsen, J.: Electrocardiographic Changes Induced by the Taking of Food, AM. HEART J. 17: 725, 1939.
5. Larsen, K., Neukirch, F., and Nielson, N. A.: Electrocardiographic Changes in Normal Adults Following Digitalis Administration, AM. HEART J. 13: 163, 1937.

6. Wilson, F. N., MacLeod, A. G., Barker, P. S., and Johnston, F. D.: The Determination and the Significance of the Areas of the Ventricular Deflections of the Electrocardiogram, *AM. HEART J.* 10: 46, 1934.
7. Rothschild, M. A., Mann, H., and Oppenheimer, B. S.: Successive Changes in the Electrocardiogram Following Acute Coronary Artery Occlusion, *Proc. Soc. Exper. Biol. & Med.* 23: 253, 1926.
8. Meira, J. A., and Ramos, J., Jr.: Considerações sobre o electrocardiograma na esquistossomíase mansoni, *Hospital, Rio de Janeiro* 26: 77, 1944.
9. Christodoss, J. D., Rajamanikam, N., and Krishnaswamy, R.: Some Observations on the Cardiovascular Action of Urea-Stibamine, *Indian J. M. Research* 21: 617, 1934.
10. Kato, K.: Ueber die pharmakologischen Wirkung von Antimon III-bis-Brenzcatechindisulfonsaurem Natrium (Fuadin) und Natrium Antimon III-bis-Protocatechusaurem. (II. Mitteilung) Wirkung auf die Herzaktion, Blutgefäße und den Skelettmuskel, *Okayama-Igakkai-Zasshi* 50: 1867, 1938.
11. Yoshimura, S.: Ueber die Digitaliswirkung auf das durch einige Antimonverbindungen geschädigte Herz, *Jap. J. M. Sc., IV, Pharmacol.* 12: 185, 1940.
12. Hassan, A.: The Distribution of Antimony in the Body Organs Following the Administration of Therapeutic Antimony, *J. Egyptian M. A.* 21: 123, 1938.
13. Boyd, T. C., Napier, L. E., and Roy, A. C.: The Distribution of Antimony in the Body Organs, *Indian J. M. Research* 19: 285, 1931.
14. Franz, G.: Zur pathologischen Anatomie der Antimonvergiftung, *Arch. f. exper. Path. u. Pharmacol.* 186: 661, 1937.
15. Magalhães, B. F., and Dias, C. B.: Esquistossomose de Manson-Estudos, *Mem. Inst. Oswaldo Cruz* 41: 363, 1944.
16. Tarr, L.: Effect of the Antimony Compounds, Fuadin and Tartar Emetic, on the Electrocardiogram. A Preliminary Report, *Bull. U. S. Army M. Dept.* 5: 336, 1946.
17. Bayley, R. H., and Monte, L. A.: Acute, Local, Ventricular Ischemia, or Impending Infarction, Caused by Dissecting Aneurysm. Case Report With Necropsy, *AM. HEART J.* 25: 262, 1943.
18. Candel, S., and Wheelock, M. C.: Acute Non-Specific Myocarditis, *Ann. Int. Med.* 23: 309, 1945.
19. Newburger, R. A., Beaser, S. B., and Shwachman, H.: A Case of Phosphorus Poisoning With Recovery Accompanied by Electrocardiographic Changes. To be published.

ORTHOSTATIC PAROXYSMAL VENTRICULAR TACHYCARDIA

CAPTAIN MICHAEL PETERS, M.C. AND CAPTAIN SIDNEY L. PENNER, M.C.
ARMY OF THE UNITED STATES

IN THE course of observations on the effect of changes in posture and various drugs on the cardiovascular system, we encountered an instance of orthostatic paroxysmal ventricular tachycardia. We believe this finding is unusual enough to warrant reporting.

REPORT OF CASE

Mrs. H. H., aged 24 years, was first seen in June, 1945, complaining of attacks of rapid heart action occurring since January, 1944. Each of these attacks began with a sensation of "pressure against the heart and gas in the stomach." The heart would then begin to beat rapidly, stop for a few beats, and then beat fast again. This was accompanied by a stuffy feeling in the ears and a sensation of blood rushing to the head. However, the attacks never occurred while the patient was lying down but appeared only in the upright position, and in this position were precipitated by excitement or mild exertion. From January, 1944, to June, 1944, attacks of rapid heart action occurred about once a month. In June, 1944, she became pregnant. The attacks were unchanged for the first five months of pregnancy, but did not recur during the remainder of the pregnancy nor during a rather difficult three-day labor. However, two weeks after delivery, she had an identical episode on getting out of bed for the first time and since then the attacks have occurred once or twice weekly. In the free intervals she has enjoyed excellent health except for "some nervousness." She has never had any dyspnea or edema. Past history included measles, mumps, chicken pox, and whooping cough in early childhood without known sequelae. There was no history of diphtheria, scarlet fever, or rheumatic fever in any of its varied manifestations. She did not use alcohol, coffee, tobacco, or any medication.

The physical examination was entirely normal. The blood pressure was 110/60. The blood count, urinalysis, and blood Kahn were normal. The basal metabolic rate was -4 per cent. X-ray examination of the heart in the posteroanterior and left lateral positions with barium in the esophagus was normal. The lung fields were clear.

Two weeks after the original consultation, the patient was seen during a spontaneous attack of tachycardia. At this time the apex and pulse rates were 150 to 180 per minute and were irregular. There were runs of rapid regular rhythm interrupted frequently by a slower rhythm. She was apprehensive and tremulous but not in acute distress.

An electrocardiogram was taken in the supine position. Leads I, II, III, and CF_2 showed brief runs of ventricular tachycardia, interrupted by one or two sinus beats. Lead CF_4 showed a normal sinus rhythm. This change to regular rhythm did not surprise the patient, who pointed out that she could always stop an attack by lying down but that the tachycardia would recur upon resuming the upright position. An electrocardiogram was therefore taken in the upright position; this record showed ventricular tachycardia once again.

On July 1, 1945, the patient stated that she had had three attacks in the preceding two weeks. Examination showed a regular sinus rhythm. After fifteen hops on each foot, she developed an attack of ventricular tachycardia proved by an electrocardiogram. Ergotamine

sulfate 0.5 mg. was given intravenously while the patient was in the standing position. She complained of feeling weak and sat down. An electrocardiogram in this position still showed ventricular tachycardia, but twenty-five minutes later the electrocardiogram showed normal sinus rhythm. When she stood up, the tachycardia did not recur, and the next day she reported no recurrence of the attacks. She was then advised to take 0.3 Gm. of quinidine sulfate daily. On July 10, 1945, she reported, by phone, that she had not had any further attacks. Unfortunately she was lost to our further observation after this date.

DISCUSSION

The diagnosis of ventricular tachycardia depends primarily on electrocardiographic findings although it can be suspected clinically. It has been shown¹ that the rhythm is not absolutely regular. Minor variations in the length of the cardiac cycle occur which can be detected by careful auscultation. In addition, there are variations in the intensity of the first heart sounds which are due to the changing time relations between auricular and ventricular systole. Close observation may also reveal *a* waves in the jugular pulse which are slower in rate than the apex beat. Further, vagal stimulation does not influence the heart rate in ventricular tachycardia as it does in paroxysmal auricular tachycardia and in auricular flutter. If auricular fibrillation is known to have existed, the sudden development of a marked rise and fall in the apex rate would suggest ventricular tachycardia, especially after heavy digitalization.²

Although ventricular tachycardia had been recognized as early as 1909,³ the criteria for the electrocardiographic diagnosis were first crystallized by Robinson and Herrmann in 1921.⁴ As amended by Cooke and White,² they include:

1. The identification of P waves during the paroxysm at a slower rate than the QRS complexes.
2. A paroxysm of abnormal ventricular complexes, i. e., three or more at a rapid rate, occurring during auricular fibrillation.
3. The onset of tachycardia with an abnormal ventricular complex.
4. A close resemblance, in the same lead, of the QRS complexes of the ventricular premature beats to the QRS complexes occurring during the tachycardia.

Only one of these conditions is needed to establish the diagnosis of paroxysmal ventricular tachycardia. The present case illustrates 3 and 4 of the criteria just given (Figs. 1 and 2). We were unable to identify P waves during the paroxysm.

Clinical Features.—Ventricular tachycardia is not a common arrhythmia. Cooke and White² found the disturbance only twenty-four times in a study of the records of 25,000 patients. Most articles on this subject report isolated cases; the largest personal series comprised thirty-six cases,⁵ while Cooke and White reported twenty-seven cases.²

Paroxysmal ventricular tachycardia is usually due to serious organic heart disease, especially coronary artery disease, but may develop after the administra-

tion of digitalis,⁶ epinephrine,^{7,8} or related drugs.⁹ It may also be induced in presumably normal hearts by chloroform¹⁰ and similar compounds.¹¹ In addition, a limited number of instances of paroxysmal ventricular tachycardia has been reported in relatively young persons with normal hearts and no external precipitating causes.^{2, 8, 12-18} Follow-up on some of these patients was continued for as long as fourteen years without developing any signs of heart disease.

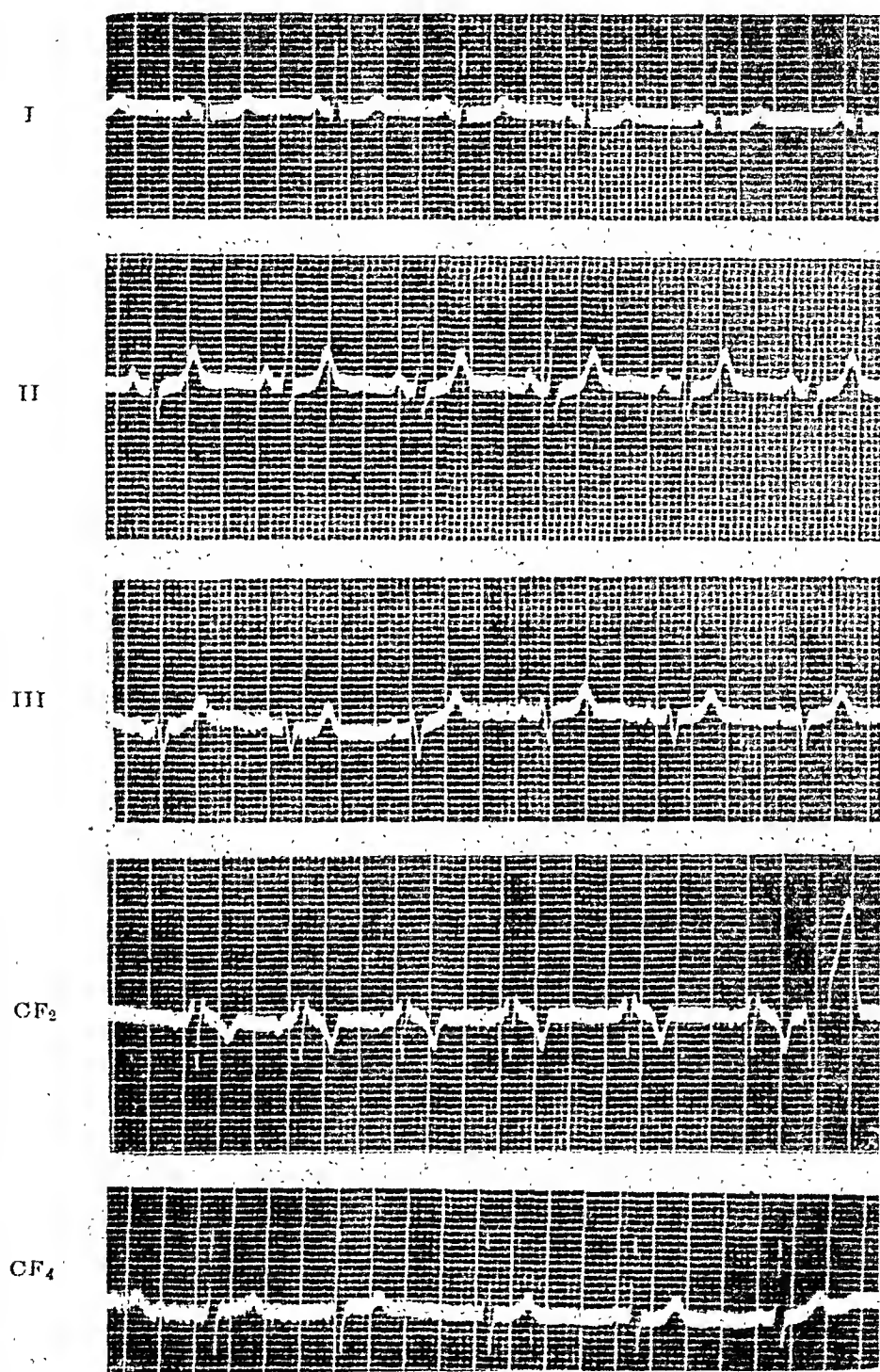


Fig. 1.—An electrocardiogram made with the patient in the supine position. The mechanism is normal.

The symptoms associated with ventricular tachycardia vary considerably, depending on the heart rate, the duration of the paroxysm, the degree and type of heart disease present, as well as the coexistence of extracardiac pathologic states. Although some subjects have no symptoms and may be unaware of the

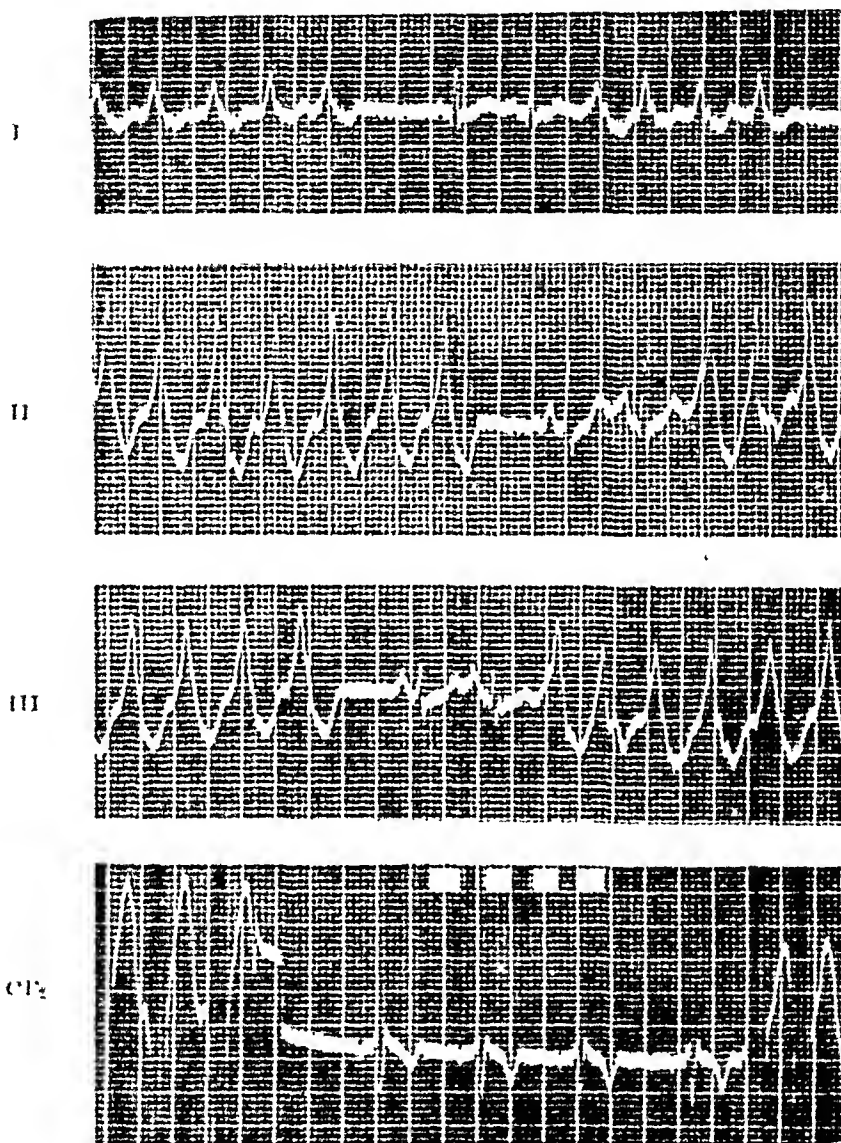


Fig. 2.—An electrocardiogram made with the patient erect shows runs of ventricular paroxysmal tachycardia interrupted by a few normal cycles.

arrhythmia, most patients complain of palpitation, precordial fluttering, or weakness. In some instances the rapid heart rate may be associated with a diminished cardiac output^{19,20} resulting in dizziness and syncope.^{11,18,22} When the ventricular rate is rapid and the paroxysm prolonged, heart failure may result, even in the absence of organic heart disease.⁸ Anginal pain may be a conspicuous feature in patients with myocardial damage, though this need not be present.²¹

In many cases, such as the one presented here, psychogenic symptoms occur as a result of repeated attacks over a long period of time in an emotionally unstable individual.

The individual paroxysm of ventricular tachycardia usually begins with isolated ventricular premature beats, followed by short runs, which finally become continuous and replace the normal sinus rhythm. The physical findings during the paroxysm which would suggest to the clinician the nature of the arrhythmia have already been outlined, as have the electrocardiographic criteria.

The prognosis of ventricular tachycardia is properly regarded as ominous, due both to the arrhythmia itself and to the almost invariably co-existent heart disease. In a group of twenty-two patients with paroxysmal ventricular tachycardia and coexisting heart disease, twenty died within two years of the first attack.² Of fifty similar cases reported by Strauss,²³ forty died within six months of the onset, with an average duration of life of twenty-four days. However, the prognosis may be regarded as more favorable in patients with chronic heart disease, in the absence of acute cardiac damage,²⁴ or when appropriate therapy is employed early in the course of the paroxysm with a favorable response.^{25,26}

In apparent contrast to this larger group of patients with organic heart disease is the limited group in whom no heart disease can be demonstrated on examination; this group appears to have a far more favorable prognosis. Cooke and White² have continued follow-up on such cases for as long as nine, twelve, and even fourteen years after the onset of paroxysms of ventricular tachycardia. However, even in this type of patient the arrhythmia carries hazards of its own, for there always remains the possibility of sudden death due, perhaps, to the development of ventricular fibrillation. Such cases have been repeatedly reported.^{27,28} Further, the development of severe⁸ or even fatal heart failure as the result of an uncontrollable attack has been recorded. With the more widespread use of appropriate therapy, including parenteral quinidine in adequate dosage,²⁹ this particular hazard may, at times, be averted. Specific criteria for a group of "benign" cases of paroxysmal ventricular tachycardia have been suggested.¹⁵ They are (1) the youth of the patient; (2) the long follow-up; (3) clinically normal hearts; (4) normal electrocardiograms during regular sinus rhythm; and (5) nomorphism of the aberrant QRS complexes during the tachycardia. However, in view of the hazard inherent in this arrhythmia, it is believed that the appellation of "benign" is inappropriate.

Physiologic Considerations.—It has long been known that sympathetic stimuli can cause ventricular tachycardia. Hoff and Nahum³⁰ were able to produce ventricular rhythms by administering adrenalin and, conversely, found that benzol poisoning, which regularly produced ventricular tachycardia, was ineffectual in the absence of the adrenal glands. Kirk and Kilpatrick⁷ reported a patient with coronary artery occlusion in whom adrenalin produced ventricular tachycardia, while Herrmann⁹ reported a similar experience with ephedrine. Furthermore, mecholyl, a parasympathomimetic drug, was found to abolish the arrhythmia in animals,³⁰ while atropine, a parasympatholytic drug, induced a paroxysm in Scott's patient.⁸

It is also recognized that the sympathetic nervous system plays an important part in the vascular adjustments taking place in man on assuming the upright position. The initial transient drop in blood pressure of 5 to 40 mm. Hg stimulates receptors in the carotid sinus, aortic arch, mesentery, and perhaps elsewhere to raise the pulse rate and bring about vasoconstriction in both the splanchnic and peripheral areas.³¹ These compensatory mechanisms are mediated by the sympathetic nervous system. In some individuals, the adjustments are inadequate and result in orthostatic hypotension,³² while in others, evidences of excessive sympathetic activity can be found. Thus, Wendkos³⁸ has reported T-wave changes in the electrocardiogram which appear on assuming the upright position and can be abolished by administering a sympatholytic drug. Comparable postural effects on the P-R interval have also been noted.^{35,36}

In the present case there was a clear-cut relation of the paroxysms of ventricular tachycardia to posture, noted both in the history and on clinical observation. Attacks occurred only in the upright position. They could always be terminated by lying down, only to recur upon reassuming the upright position. Further, the attacks could be readily precipitated by exertion or excitement, factors which are known to be associated with increased sympathetic tone.³⁷ In several case reports of "benign" ventricular tachycardia, one finds notations that the attacks were precipitated by exertion,^{8,14,27} while in one of these cases⁸ it was noted that the paroxysms were occasionally relieved by the supine position, resembling our case in this respect. A similar experience in two cases of auricular tachycardia has been reported.³⁴ It is interesting to note that our patient had no attacks in the last trimester of pregnancy, at a time when increased intra-abdominal pressure and increased blood volume would tend to minimize the reflexes ordinarily active on assuming the upright position.

These considerations, therefore, made it appear likely to us that the attacks of paroxysmal ventricular tachycardia were due to unusually strong sympathetic tone produced by assuming the upright position, by exertion, or by excitement. With this thought in view, the patient was given an intravenous injection of 0.5 mg. of ergotamine tartrate during a paroxysm. Within twenty-five minutes the attack ceased and could not be reproduced thirty minutes later by the assumption of the upright position. Since the pharmacologic action of ergotamine in this dosage is sympatholytic,³¹ the result obtained would support the view that autonomic imbalance is the cause of the tachycardia. Unfortunately, we did not have an opportunity to try mechohyl which was used in animals by Hoff and Nahum.³⁰ Pertinent to this problem is Scott's observation that atropine, a parasympatholytic drug, induced a paroxysm of ventricular tachycardia in his patient. Had a parasympathomimetic drug been used effectively in our case, the role of the autonomic nervous system in the causation of this arrhythmia related to posture would have been strengthened. The fact that mechohyl was used unsuccessfully in the unusual case recently reported by Chapman³⁹ does not invalidate these conclusions.

SUMMARY

An unusual instance of orthostatic paroxysmal ventricular tachycardia in a young woman with no other evidence of heart disease is reported. The relation to autonomic imbalance is discussed.

REFERENCES

1. Levine, S. A., and Strong, G. F.: Irregularity of Ventricular Rate in Paroxysmal Ventricular Tachycardia, *Heart* 10: 125, 1923.
2. Cooke, W. T., and White, P. D.: Paroxysmal Ventricular Tachycardia, *Brit. Heart J.* 5: 33, 1943.
3. Lewis, Thomas: *The Mechanism of the Heart Beat*, London, 1911, Shaw & Sons, Ltd.
4. Robinson, G. C., and Herrmann, G. R.: Paroxysmal Tachycardia of Ventricular Origin and Its Relation to Coronary Occlusion, *Heart* 8: 59, 1921.
5. Williams, Conger, and Ellis, Lawrence B.: Ventricular Tachycardia; an Analysis of 36 Cases, *Arch. Int. Med.* 71: 137, 1943.
6. Marvin, H. M.: Paroxysmal Ventricular Tachycardia With Alternating Complexes Due to Digitalis Intoxication, *AM. HEART J.* 4: 21, 1928.
7. Kirk, Robert C., and Kilpatrick, E. M.: Ventricular Tachycardia From Adrenalin and Sinus Standstill From Intravenous Quinidine in Case of Coronary Occlusion, *Ohio State M. J.* 37: 437, 1941.
8. Scott, R. W.: Observations on a Case of Ventricular Tachycardia With Retrograde Conduction, *Heart* 9: 297, 1922.
9. Herrmann, George R.: Disturbance of the Heart Beat, in *Stroud's Diagnosis and Treatment of Cardiovascular Disease*, Philadelphia, 1945, F. A. Davis Company.
10. Hill, I. G. W.: Cardiac Irregularities During Chloroform Anaesthesia, *Lancet* 1: 1139, 1932.
11. Geiger, Arthur J.: Cardiac Dysrhythmia and Syncope, *J. A. M. A.* 123: 141, 1943.
12. McMillan, Thomas M., and Bellett, Samuel: Ventricular Paroxysmal Tachycardia: Report of a Case in a Pregnant Girl of 16 Years With an Apparently Normal Heart, *AM. HEART J.* 7: 70, 1931.
13. Routier, D.: Benign Ventricular Extrasystole With Paroxysmal Tachycardia, *Arch. d. mal du coeur* 30: 224, 1937.
14. Anderson, Maine C.: Paroxysmal Ventricular Tachycardia, *Am. J. M. Sc.* 181: 309, 1931.
15. Routier, Daniel, and Puddu, Vittorio: Benign Ventricular Extrasystole With Paroxysmal Tachycardia; 2 Clinical Cases, *Arch. d. mal. du coeur* 29: 676, 1936.
16. Cassinis, Ugo, and Sibilia, Daniele: Benign Juvenile Ventricular Tachycardia, *Cuore e circolaz.* 25: 148, 1941.
17. Bramwell, C., and King, J. T.: *Principles and Practice of Cardiology*, London, 1942, Oxford University Press.
18. Marra, Alfred F.: Report of a Case of Paroxysmal Ventricular Tachycardia, With No Demonstrable Organic Heart Disease, Which Produced Attacks of Syncope, *AM. HEART J.* 28: 810, 1944.
19. Wiggers, Carl J.: *Physiology in Health and Disease*, ed. 2, Philadelphia, 1937, Lea & Febiger.
20. Stewart, H. J., Deitrick, J. E., Crane, N. F., and Thompson, W. P.: Studies of the Circulation in the Presence of Abnormal Cardiac Rhythms, *J. Clin. Investigation* 17: 449, 1938.
21. Wolff, Louis: The Cardinal Manifestations of Paroxysmal Tachycardias. I. Anginal Pain, *New England J. Med.* 232: 491, 1945.
22. Wolff, Louis: The Cardinal Manifestations of Paroxysmal Tachycardias. II. Vascular Collapse, *New England J. Med.* 232: 527, 1945.
23. Strauss, Maurice B.: Paroxysmal Ventricular Tachycardia, *Am. J. M. Sc.* 179: 337, 1930.
24. Riseman, Joseph E. F., and Linenthal, Harry: Paroxysmal Ventricular Tachycardia, *AM. HEART J.* 22: 219, 1941.
25. Dubbs, Alfred W., and Parmet, David H.: Ventricular Tachycardia Stopped on the 21st Day by Giving Quinidine Sulfate Intravenously, *AM. HEART J.* 24: 272, 1942.

36. McMillan, R. L.: Ventricular Tachycardia as a Therapeutic Problem in Coronary Thrombosis, *South. M. J.* 36: 800, 1943.
37. Wilson, F. H., Wishart, S. W., MacLeod, A. G., and Barker, P. S.: A Clinical Type of Paroxysmal Tachycardia of Ventricular Origin in Which Paroxysms Are Induced by Exertion, *AM. HEART J.* 8: 155, 1932.
38. Campbell, M., and Elliott, G. A.: Paroxysmal Tachycardia; Aetiology and Prognosis of 100 Cases, *Brit. Heart J.* 1: 123, 1939.
39. Reich, Nathaniel E.: Successful Use of a Massive Dose of Quinidine in a Case of Intractable Ventricular Tachycardia, *AM. HEART J.* 28: 256, 1944.
40. Hoff, H. E., and Nahum, Louis H.: The Role of Adrenalin in the Production of Ventricular Rhythms and Their Suppression by Acetyl-B-Methyl-Choline Chloride, *J. Pharmacol. & Exper. Therap.* 52: 235, 1934.
41. Abramson, David I.: Vascular Responses in the Extremities of Man in Health and Disease, Chicago, 1944, University of Chicago Press.
42. Bradbury S., and Eggleston, C.: Postural Hypotension, *AM. HEART J.* 1: 73, 1925.
43. Goodman, L., and Gilman, A.: The Pharmacologic Basis of Therapeutics, New York, 1941, The Macmillan Co.
44. Miller, Ralph, and Perelman, Julius S.: Chronic Auricular Tachycardia With Unusual Response to Change in Posture, *AM. HEART J.* 29: 555, 1945.
45. Alexander, H. L., and Bauerlein, T. C.: Influence of Posture on Partial Heart-Block, *AM. HEART J.* 11: 223, 1936.
46. Manning, G. W., and Stewart, C. B.: Alteration in P-R Interval Associated With Change in Posture, *AM. HEART J.* 30: 109, 1945.
47. Weiss, Soma: The Interaction Between Emotional States and the Cardiovascular System in Health and in Disease, Contributions to the Medical Sciences in Honor of Dr. Emanuel Libman by His Pupils, Friends, and Colleagues, New York, 1932, International Press, Vol. 3, p. 1181.
48. Wendkos, Martin H.: The Influence of Autonomic Imbalance on the Human Electrocardiogram, *AM. HEART J.* 26: 549, 1944.
49. Chapman, Don W.: Observations On Two Patients With Paroxysmal Ventricular Tachycardia Treated by the Intravenous Administration of Quinidine Lactate, *AM. HEART J.* 30: 276, 1945.

Clinical Reports

ANEURYSM OF THE DESCENDING THORACIC AORTA

SAMUEL A. LOEWENBERG, M.D., and SAMUEL BAER, M.D.
PHILADELPHIA, PA.

BECAUSE of the comparative rarity of aneurysms of the lower thoracic aorta and because the diagnosis is frequently missed, we feel justified in discussing this condition and reporting such a case. Most reported series of aortic aneurysms are divided into three groups; that is, those of the arch, of the thoracic aorta, and of the abdominal aorta. Of these, aneurysms of the descending thoracic aorta are the least common.

Lucke and Rea,¹ in their series of 321 aortic aneurysms, found that 173 were in the arch, 40 in the abdominal, and 31, or 11.7 per cent, in the thoracic aorta. Of these, the number of lower thoracic aneurysms were found to be comparatively few. Brindley and Schwab² stated that 2 per cent of aortic aneurysms were found in the lower thoracic aorta, and Kampmeier³ noted 30 of 633 aortic aneurysms (4.7 per cent) were in the descending thoracic aorta. Levitt and Levy⁴ reported about the same incidence; of ninety-four aortic aneurysms, four were found in the descending thoracic aorta.

Not only are these aneurysms of the thoracic aorta rare, but, because of their location and because of the varied clinical pictures which they produce, they may frequently remain undiagnosed during life. Nonetheless, a review of the literature suggests that the clinical features and roentgen findings in most instances are sufficiently characteristic to warrant the diagnosis of aneurysm of the descending aorta.

CASE HISTORY

W. B., a colored man 61 years of age, complaining of abdominal pain, was admitted Feb. 11, 1944, to the Philadelphia General Hospital on the surgical service. The patient had been in his usual state of health until Jan. 23, 1944, when he first noted weakness and general malaise and a slight cough. A physician told him he had "flu" and recommended bed rest. About a week after the onset of the illness he began having abdominal pain. The pain was located in the upper abdomen just above the umbilicus. It was dull but persistent and was aggravated by coughing and deep breathing. The remainder of the present history was essentially negative. The previous history revealed that in 1941, upon admission for a suprapubic prostatectomy, a strongly positive Wassermann had been found.

The patient appeared quite comfortable. The temperature was 100.4° F.; the pulse rate, 100 per minute; the respiratory rate, 20 per minute; and the blood pressure, 120/80. The other

From the Medical Service of Dr. Samuel A. Loewenberg, Philadelphia General Hospital.
Received for publication Oct. 29, 1945.

significant findings were a few crackling râles in the right lower lung posteriorly and moderate tenderness bilaterally in the upper abdomen. A tentative diagnosis of influenza or subacute cholecystitis was made. On Feb. 12, 1944, a cholecystogram and a routine chest x-ray film were negative. In view of the absence of physical signs and of significant laboratory findings suggesting a surgical diagnosis, the patient was transferred to the medical service.

When first seen in the medical wards, the patient did not appear acutely ill. He continued to run a temperature fluctuating between 99 and 102° Fahrenheit. Physical examination revealed somewhat sluggish pupils, tremors of the hands, an impaired percussion note, and a few moist râles in the right upper lobe posteriorly. A diagnosis of subsiding pneumonitis of the right upper lobe was considered.

The Wassermann reaction was reported positive on two occasions. The interpretation of a second cholecystogram done March 1, 1944, was "nonvisualization of the gall bladder." The spinal fluid was found to be completely normal. Blood sugar and blood urea were normal, urine and blood cultures were sterile, and agglutination studies for typhoid, paratyphoid, and undulant fever were negative. A blood count revealed 3,000,000 erythrocytes and 13,400 leucocytes, of which 72 per cent were polymorphonuclear cells. A gastrointestinal series was begun March 14, 1944. Upon fluoroscopy and roentgen study of the esophagus and stomach, it was noted that the esophagus in its lower portion was displaced anteriorly and to the left by a mass lying anterior and to the right of the spine. Fluoroscopically this lesion appeared to be continuous with the descending aorta. X-ray examination of the spine showed suggestive evidence of erosion of the bodies of the ninth and tenth dorsal vertebrae on the right (Figs. 1, 2, and 3). Based on these findings a diagnosis of aneurysm of the descending aorta was made. Because of the unusual displacement of the esophagus, it was assumed that the aneurysm was located in the lower thoracic aorta as it entered the hiatus of the diaphragm.

The patient's condition became progressively worse. His cough became more severe and he expectorated bright red blood. The cough was present only in the morning and on one occasion was accompanied by the expectoration of a cupful of bright red blood. The temperature continued elevated, but with sedation the cough and hemoptysis subsided. On the morning of March 21, 1944, the patient was suddenly seized with a severe paroxysm of coughing with profuse hemoptysis and died before a physician could reach his bedside.

Autopsy.—Autopsy was performed four hours post mortem. The body was that of a well-developed, well-nourished, middle-aged Negro man. There was a suprapubic cystotomy scar. Slight axillary and inguinal lymphadenopathy was noted.

Approximately 250 c.c. of clear, straw-colored fluid were found in the right pleural cavity and about 100 c.c. in the left pleural cavity. There appeared to be approximately from 150 to 200 c.c. of pericardial fluid which was not well measured and about 750 c.c. of slightly opalescent fluid in the peritoneal cavity. There were a few adhesions between the gall bladder and the mesentery of the transverse colon. The peritoneal surfaces were otherwise smooth and glistening. The dome of the urinary bladder was adherent to the anterior abdominal wall beneath the site of the cystotomy wound. The aorta showed tree-bark wrinkling throughout and many atherosclerotic plaques. The mouths of the coronary arteries were widely patent. The ascending portion of the arch was somewhat dilated. At the lowermost portion of the descending aorta just above the diaphragm, a large saccular aneurysm was found. The ostium of the aneurysm measured 6 cm. in diameter and seemed completely filled with a thrombus. The thrombus and sac measured 10 cm. in diameter and extended into the left pleural cavity, pressing upon the left lower lobe. The pleura here was adherent to the aneurysmal sac which had ruptured into the lung tissue at the base of the sac. The heart appeared normal in size. The myocardium showed gross fibrosis. The aortic valve cusps were thin and mobile. The sinuses of Valsalva were somewhat stretched due to dilatation of the aorta. The mitral valve leaflets showed a few thickened areas. The coronary arteries had a minimal amount of sclerosis but appeared normal otherwise.

The left lung weighed 463 grams; the right, 510 grams. The lungs revealed smooth and glistening pleural surfaces, beneath which areas of hemorrhage could be seen. There was a fine

generalized emphysema which made the lungs pillowy to palpation. The sectioned surfaces showed the bronchi to be filled with blood which was clotted. The pulmonary tissue showed diffusely scattered blood-red areas due apparently to aspiration of blood in the alveoli. A probe passed through the bronchus of the right lower lobe entered the area at the base where the aneurysm had ruptured into the lung; this area was apparently the source of the blood in the bronchial tree. The pulmonary vessels were patent.



Fig. 1.—Note the shadow of the aortic aneurysm behind the cardiac silhouette.

The spleen weighed 80 grams and was normal in size. Its sectioned surface showed the follicular markings well against a blood-red pulp. The axillary, inguinal, and mesenteric lymph nodes were slightly enlarged and rubbery in consistency.

The left kidney weighed 190 grams; the right, 170 grams. The kidneys appeared normal in size. Their capsules stripped with slight difficulty to reveal a finely granular surface which retained some degree of fetal lobulation and also showed a few small, red, shallow, depressed scars. The sectioned surfaces showed congestion. The markings of the cortex and medulla appeared grossly normal in outline and ratio. The renal pelvis were thickened. The ureters showed slight thickening of their walls. The right renal pelvis was subdivided and terminated in a double ureter which united at a point approximately located at the edge of the pelvic brim. The urinary

bladder was adherent to the anterior abdominal wall. There appeared to be a scar on the left side of the bladder fundus. The bladder mucosa was congested. The left testicle was one-half the size of the right, which appeared normal in size. There was a scar in the midline at the base of the bladder extending into the prostatic urethra.



Fig. 2.—As seen in the anteroposterior view, the esophagus is displaced to the left and anteriorly. The shadow of the barium-filled esophagus has been retouched.

The esophagus showed interesting findings; it had an S-shaped course. At the top of the upper edge of the aneurysm the esophagus was displaced horizontally, and at the lower portion of the aneurysm the esophagus was pushed by it to the left. The stomach contained approximately 250 c.c. of clotted blood. There were scattered petechiae and mucosal hemorrhages throughout the intestines. The liver weighed 1,200 grams and was congested. Its margins were slightly rounded. The lobular markings were well defined. There were a few adhesions around the gall bladder. It contained normal, concentrated bile. The bile ducts were patent. The pancreas appeared rather large and firm but was otherwise normal.

The adrenals appeared normal. The brain was not removed.

Summary.—(1) Syphilitic aneurysm of the descending thoracic aorta; (2) rupture of the aneurysm into the left lung, emphysema; (3) distortion of the esophagus; and (4) benign nephrosclerosis, healed pyelonephritis, double right ureter.



Fig. 3.—In the right oblique view, the anterior displacement of the esophagus is readily visible. The shadow of the barium-filled esophagus has been retouched.

DISCUSSION

The varied abdominal syndromes produced by thoracic disturbances as a whole, and by aortic aneurysms in particular, have been repeatedly reported. Coronary thrombosis, dissecting aneurysm, aortic lesions, pleurisy, pulmonary malignancy, and pneumonia have all masqueraded as primary gastrointestinal disease. Loewenberg and March⁵ reported on a patient with aneurysm of the lower thoracic aorta in whom the sole symptom was persistent and intractable hiccup. Interestingly enough, this aneurysm also occurred at the hiatus of the diaphragm and was diagnosed premortem.

The anatomic relation of the esophagus to the aorta is of extreme importance in diagnosing the lesion. Roesler⁶ and others have emphasized the value of determining the displacement of the barium-filled esophagus in cardiac roentgenology. Normally, the upper thoracic aorta occupies a position anterior and to the left of the esophagus. As the aorta and esophagus pass through the hiatus

of the diaphragm, the esophagus crosses over the aorta, at this point being anterior and somewhat to the left of the aorta. In the majority of aortic aneurysms, the aortic extension is posteriorly and to the left,⁷ so that the esophagus is displaced posteriorly and to the right. The only aortic aneurysm that can displace the esophagus anteriorly and to the left is in an aorta at the hiatus. Roesler⁶, Shanks, Kerley, and Twining,⁸ and others⁹⁻¹² have stressed this anatomic relationship and have pointed out that this deviation of the esophagus may be produced by one other rare aortic abnormality; namely, right-sided aortic arch.

Another finding of note was the erosion of the ninth and tenth dorsal vertebrae. Many observers,^{5, 6, 13} in commenting on aneurysms of the lower aorta, have emphasized the roentgen finding of destruction of the ninth, tenth, eleventh, and twelfth dorsal and the first lumbar vertebrae. In the majority of cases of aneurysm of the descending aorta, this is a nearly constant finding demonstrable by x-ray examination.

CONCLUSIONS

1. The relative incidence of aneurysms at various aortic sites is reviewed and a case of aneurysm of the descending thoracic aorta reported.
2. The clinical and roentgen features of this rare aneurysm are discussed.
3. Gastrointestinal syndromes produced by this lesion are mentioned and the relation of the esophagus to the aorta emphasized. Attention is also called to erosion of the vertebrae produced by aneurysm of the descending thoracic aorta.

REFERENCES

1. Lucke, B., and Rea, M. H.: Studies on Aneurysm, *J. A. M. A.* 77: 935, 1921.
2. Brindley, P., and Schwab, E. H.: Aneurysms of the Aorta, *Texas State J. Med.* 25: 757, 1930.
3. Kampmeier, R. H.: Saccular Aneurysm of the Thoracic Aorta, *Ann. Int. Med.* 12: 624, 1938.
4. Levitt, A., and Levy, D. S.: Aneurysm of the Thoracic and Abdominal Aorta, *Am. J. Clin. Path.* 10: 332, 1940.
5. Loewenberg, S. A., and March, H. C.: Persistent Hiccoughs as the Sole Symptom of Thoracic Aneurysm, *AM. HEART J.* 13: 624, 1937.
6. Roesler, Hugo: *Clinical Roentgenology of the Cardiovascular System*, Springfield, Ill., 1943, Charles C. Thomas.
7. Lucke, B., and Rea, M. H.: Studies on Aneurysm, *J. A. M. A.* 81: 1167, 1923.
8. Shanks, S. C., Kerley, P. J., and Twining, E. W.: *Textbook of X-ray Diagnosis*, vol. 1, London, 1938, H. K. Lewis & Co., Ltd.
9. Isard, H. J.: Right-Sided Aortic Arch, *U. S. Nav. M. Bull.* 42: 168, 1944.
10. Friedman, M.: Right-Sided Aorta; Report of Two Cases, *Radiology* 25: 106, 1935.
11. Metzger, H. N., and Ostrum, H. W.: Right Sided Aortic Arch, *Am. J. Digest. Dis.* 6: 32, 1939.
12. Eisen, D., and Taub, H. N.: Right Sided Aortic Arch, *Canad. M. A. J.* 45: 402, 1941.
13. Putts, B. S., and Bacon, R. D.: Large Aneurysms of the Thoracic Aorta, *Am. J. Roentgenol.* 35: 59, 1936.

HEART BLOCK CAUSED BY FAT INFILTRATION OF THE INTER-VENTRICULAR SEPTUM (COR ADIPOSUM)

DAVID M. SPAIN, M.D., and RICHARD T. CATHCART, M.D.
NEW YORK, N. Y.

The condition of "fatty heart," which has also been called at various times lipomatosis cordis, fatty infiltration of the myocardium, and cor adiposum, was a frequent clinical diagnosis over twenty-five years ago. In more recent years, this diagnosis has fallen into disrepute. Although it is true that "fatty heart" only rarely causes actual clinical manifestations of disturbed cardiac function, it is a definite entity that on occasion may not only be responsible for clinical evidence of heart disease, but may also be the sole important factor leading to the death of the individual.

Corrigan and Saphir* studied the anatomic changes in this condition. Their report consists of an analysis of fifty-eight necropsied cases that revealed anatomic evidence of fatty infiltration of the myocardium. Fat infiltration most likely originates from pre-existing, subepicardial fat. The usual site of infiltration is into the myocardium of the right ventricle. At times the myocardium may be completely replaced, or at least the few remaining fibers may be compressed as a result of the fat infiltration. The left ventricle is only occasionally involved and never to any significant degree. Isolated patches of fat are infrequently found beneath the endocardium of the left or right ventricle. At times fat may infiltrate down from the base of the heart into the interventricular septum. Because of the isolated patches occasionally found beneath the endocardium, it has been postulated that the fat originated not from direct infiltration, but as a result of transformation of pre-existing fibrocytes in situ into fat cells.

Corrigan and Saphir attributed the death of two of their patients solely to the fat infiltration. In twenty-nine of their patients important contributory symptoms were explained on this condition, while in the remaining twenty-three it was considered merely an incidental finding. It should be noted that fat infiltration is not to be confused with fatty degeneration that is secondary to infectious or anemic states.

The purpose of this report is to describe a case in which it is believed the manifestations of heart disease that consisted of right-sided heart failure and heart block were caused by fat infiltration of the right ventricular myocardium

From the Laboratory of Pathology, Bellevue Hospital, and First Medical Division, Bellevue Hospital, (Columbia University, College of Physicians and Surgeons).

Received for publication Oct. 20, 1945.

*Corrigan, M., and Saphir, O.: Fatty Infiltration of the Myocardium, Arch. Int. Med. 52: 410, 1933.

and the interventricular septum. A careful search through the literature has failed to disclose any previously reported case of heart block caused by fat infiltration of the myocardium.

CASE REPORT

The patient, a 59-year-old white woman, housewife, was admitted to the First Medical Division of Bellevue Hospital, May 9, 1944, with the complaint of difficulty in breathing of five hours' duration. For nineteen years prior to admission she had noted transient swelling of the ankles. Recently this had been occurring at more frequent intervals and finally became constant. Twelve years prior to admission, she had a single attack of precordial, knifelike pain that continued for several hours. At that time her physician told her she had a heart attack and gave her digitalis for several weeks. She has never again had a similar attack. During the last five years, she has complained of frequent attacks during which "everything would go black, her heart would pound hard and fast," and there would be difficulty in breathing. These attacks were irregular, occurring either at rest or during activity, and lasted from several minutes to several hours. They seemed to be shortened following an injection by her physician; the nature of this injection could not be ascertained. For the past two years, the difficulty in breathing became constant and she was again given digitalis which she continued to take until this admission. The immediate episode that brought her to the hospital began while she was asleep. She was awakened by palpitation and dyspnea of an extremely severe character.

Physical examination on admission revealed an extremely obese, well-developed, 58-year-old white woman, slightly dyspneic and cyanotic. The head and neck were normal. The neck veins were not engorged. The lungs were normal. The left border of the heart was 15 cm. to the left of the mid-sternal line with the apex in the fifth intercostal space. The heart sounds were extremely distant with P_2 greater than A_2 . There was a soft blowing systolic murmur heard best at the base. The rate was irregular and varied between 40 and 80; however, there was no pulse deficit. The abdomen was obese but otherwise not remarkable; no organs were felt. Slight pitting edema was present in both lower extremities. The remainder of the physical examination revealed nothing of significance.

The temperature on admission was 99.4°F ., the pulse varied between 40 and 80, and the blood pressure was 108/68. The leucocyte count was 8,250, with 69 per cent polymorphonuclear leucocytes, 30 per cent lymphocytes, and 1 per cent eosinophilic leucocytes. Hemoglobin (Sahli) was 13 grams. Examination of the urine was normal. The erythrocyte sedimentation rate was 9 mm. in one hour. The Wassermann reaction was negative. The blood cholesterol was 286 mg. per cent. The basal metabolic rate was plus 6 per cent. The patient's weight was 187 pounds. Venous pressure measured 140 mm. of water. The circulation time, arm-to-tongue, was 22 seconds; arm to lung, 10 seconds. An electrocardiogram on admission showed marked left-axis deviation; auricular rate, 80; ventricular rate, 40; P-R₂, 0.22 second; QRS, 0.12 seconds; T₂ inverted (Fig. 1).

The patient responded moderately well to bed rest. The edema lessened with diuresis. The four-month stay in the hospital was characterized by many episodes that were apparently similar to the attacks she had had prior to admission. These attacks were of two types; each was accompanied by a moderate amount of cyanosis. During one, however, she would be markedly apprehensive and dyspneic without any change in physical signs. In particular, there would be no change in cardiac rate and no loss of consciousness. The second type would be more severe. During these attacks the patient would become comatose and the heart sounds would be almost impossible to hear. The heart rate on several occasions was markedly decreased. Asystole was never definitely noted, and there were never any convulsive seizures. Following these latter attacks, the patient would be entirely normal after a period of fifteen minutes and would lie quietly in bed for most of the day thereafter. The first type of attack was sometimes relieved by a sedative or a placebo. The second type was relieved by epinephrine. Repeated electrocardio-

grams revealed slightly variable but more or less constant heart block. The attacks first occurred about every ten days, but the interval between them tended to become shorter, and occasionally the attacks occurred several times in one day. Epinephrine relieved her for a time but later was of no value. Barium chloride had a similar effect. The patient was then given digitalis. Subjectively she felt better. During the first day of digitalization she had several mild attacks but thereafter was asymptomatic for two weeks. She then had a severe attack, following which the electrocardiogram revealed a complete heart block with a ventricular rate of 22 (Fig. 2). Thereafter she remained asymptomatic for one week, apparently none the worse for

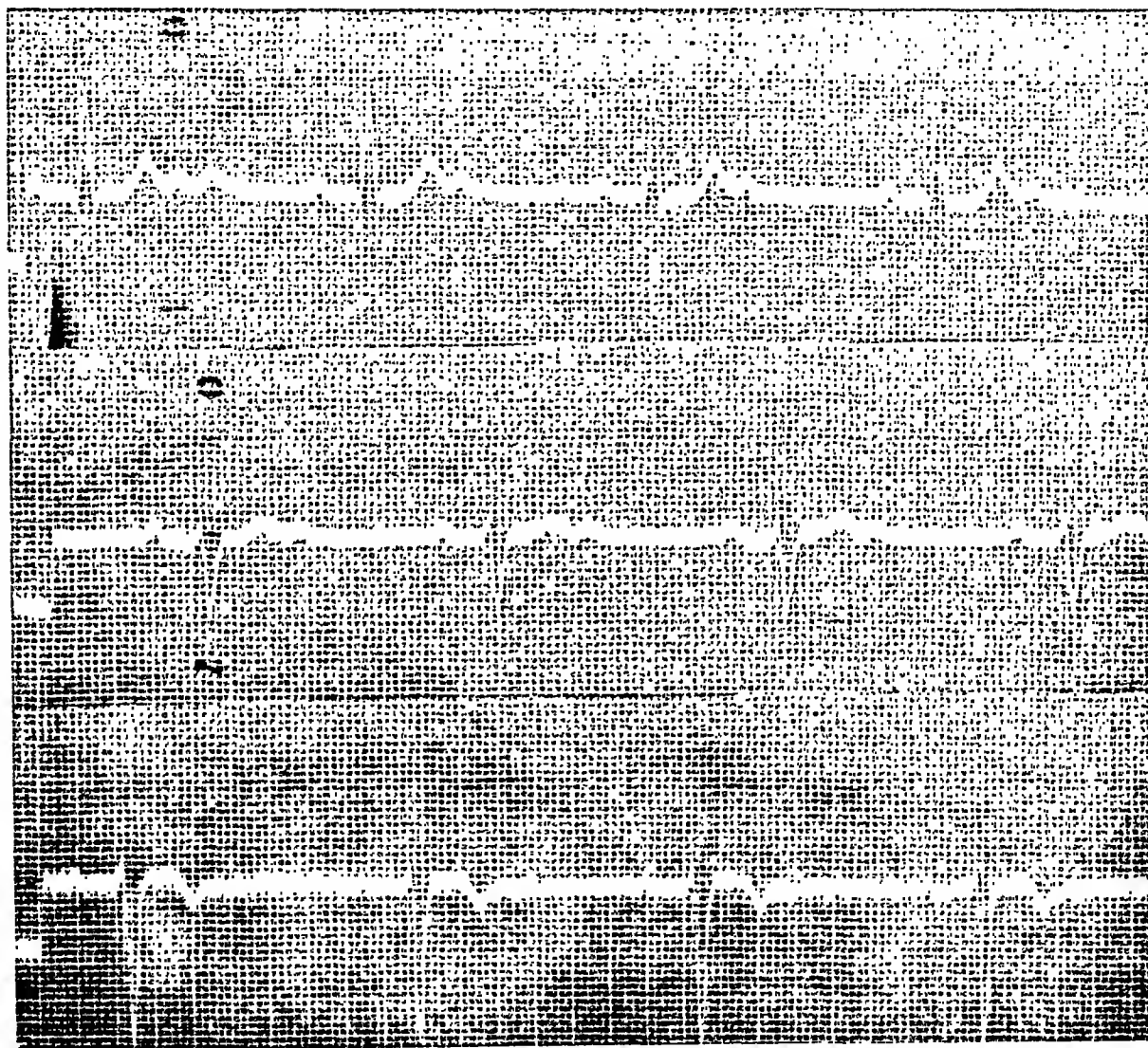


Fig. 1.—Electrocardiogram taken on admission revealing an auricular rate of 80 and a ventricular rate of 40.

the slow heart rate. Finally, on the one hundred tenth hospital day, she experienced another severe attack from which she did not recover despite the administration of epinephrine, coramine, and oxygen.

*Post-Mortem Examination** (Necropsy No. 32655).—The body was that of a well-nourished, extremely obese, elderly white woman, 5 feet, 3 inches in height, and weighing approximately 190 pounds. Marked dependent lividity was present and there was slight edema of the ankles.

*Description is limited to the pertinent findings.

The panniculus was everywhere quite thick and golden yellow in color. The heart weighed 570 grams. The epicardium was smooth and glistening, and there was a marked increase of sub-epicardial fat. Fat extended directly into the myocardium of the right ventricle and practically replaced all of the muscle fibers. This also was present to an insignificant degree in the left ventricle. Numerous sections through the interventricular septum, particularly in the region of the auriculoventricular node, revealed almost the entire myocardium to be replaced by fat. No similar change was present in the lower two-thirds of the interventricular septum. All of the chambers were dilated and the walls were flabby. The valve leaflets were all delicate and competent. The foramen ovale was not patent. The coronary ostia were widely patent and the coronary arteries were without evidence of atherosclerosis. The aorta was not dilated or tortuous and the wall was elastic. There were a moderate number of atheromatous plaques present.

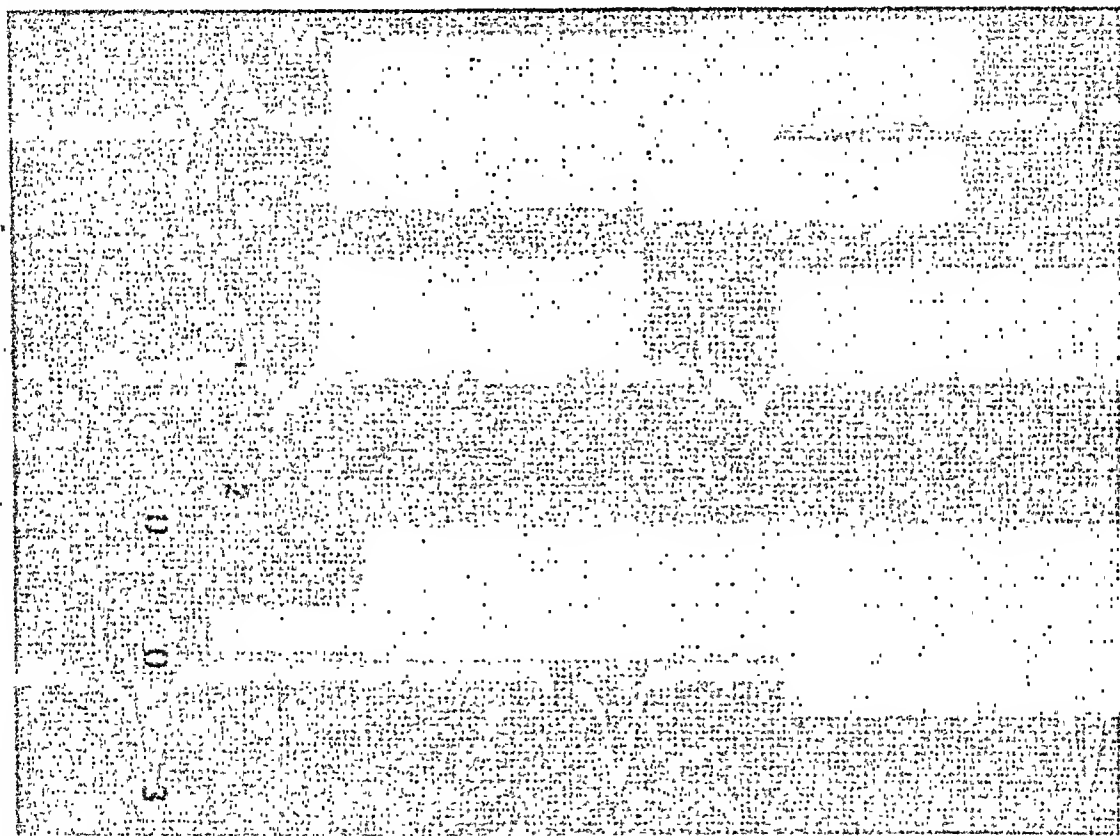


Fig. 2.—Electrocardiogram taken two weeks after digitalization revealing complete heart block with a ventricular rate of 22.

The lungs were congested. The liver weighed 2,000 grams and the lobular architecture was accentuated. The cut surface was deep red in color. The only other abnormal finding was the absence of both ovaries and Fallopian tubes (surgical).

Examination of histologic sections from the right ventricle and interventricular septum disclosed almost complete replacement of the myocardial fibers by fat cells (Fig. 3). Wherever myocardial fibers persisted, they were markedly compressed. The final anatomic diagnosis was obesity; fat infiltration of the myocardium, most marked in the right ventricle and interventricular septum; enlargement of the heart; atrophy of the myocardium; chronic passive congestion of the liver; congestion of the spleen; edema of the lungs; edema of the ankles; absence of both tube and ovaries.

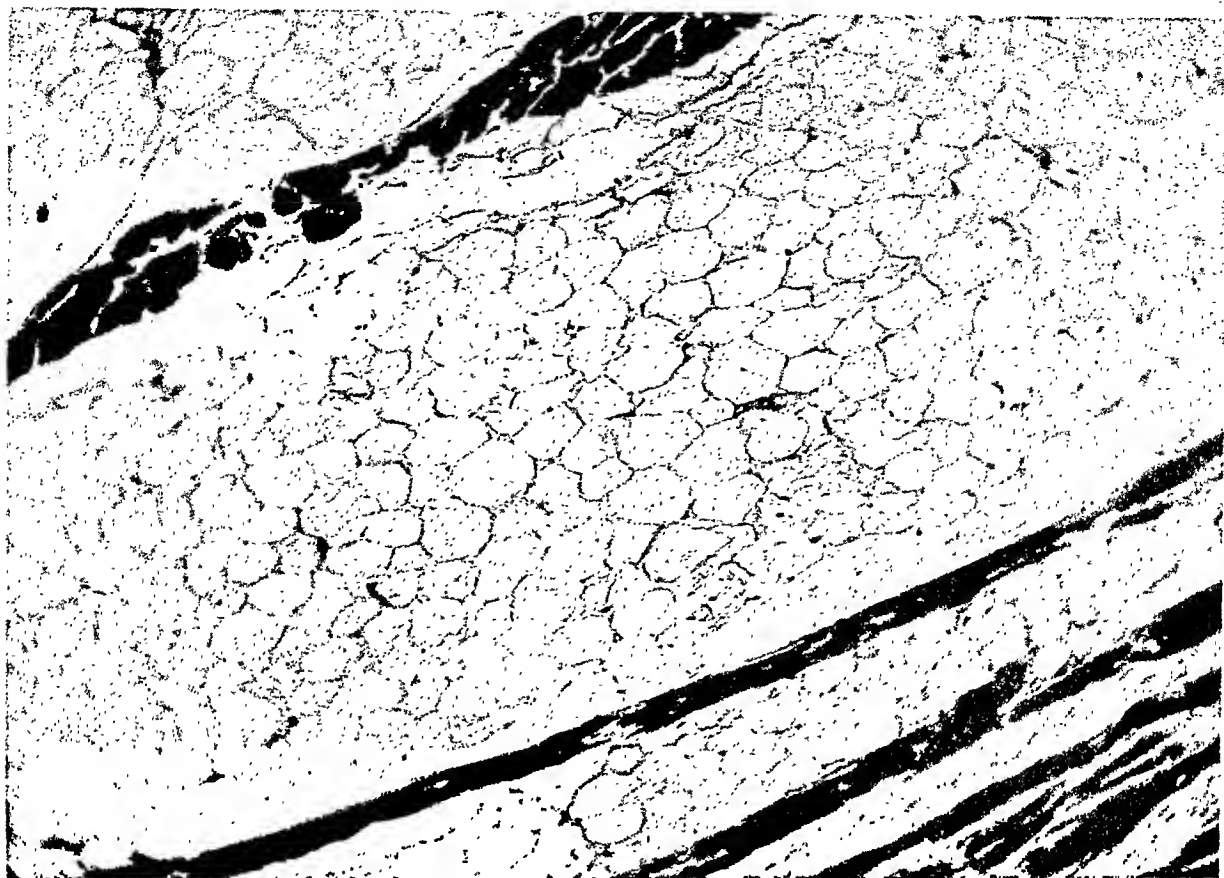


Fig. 3.—Photomicrograph of section taken through interventricular septum revealing extensive fat infiltration with compression of remaining myocardial fibers (hematoxylin and eosin, X80).

DISCUSSION

Post-mortem examination of the heart revealed no evidence of rheumatic, syphilitic, hypertensive, or arteriosclerotic disease. In addition, there was no clinical evidence of avitaminosis or anemia, and the basal metabolic rate was plus 6. It, therefore, seems reasonable to assume that the clinical manifestations of heart failure that were present for many years can best be explained by the interference of the function of the right ventricle subsequent to the fat infiltration. Although heart block does occur without any demonstrable anatomic change in the heart, the extensive infiltration of the fat in the upper third of the interventricular septum undoubtedly played an important role in the development of the heart block in this patient.

Fat infiltration of the heart is most commonly associated with obesity, diabetes mellitus, and chronic alcoholism. In this particular case, the patient was very obese with extensive deposits of fat beneath the epicardium in the omentum and mesentery. This case differed somewhat in clinical course from that of the usual case of "fatty heart" in that the heart failure was chronic, and also in that heart block was present. On rare occasions the complete replacement of the myocardium of the right ventricle may so weaken the wall that rupture takes place.

SUMMARY

A case of extensive fat infiltration of the right ventricle and interventricular septum of the heart is presented. *

The clinical manifestations of chronic right-sided heart failure and heart block is attributed to this anatomic change.

SYPHILITIC GUMMATOUS AORTITIS AS THE CAUSE OF CORONARY ARTERY OSTIAL STENOSIS AND MYOCARDIAL INFARCTION

REPORT OF A CASE

TOBIAS WEINBERG, M.D., AND HEINZ F. BEISSINGER, M.D.
BALTIMORE, MD.

ALTHOUGH syphilitic aortitis per se is frequently observed at necropsy, the gummatous type of involvement is admittedly rare.^{1,2} Furthermore, the association of coronary artery ostial stenosis and myocardial infarction is itself uncommon,³ so that this association in a case of gummatous aortitis makes the following case even more unusual and prompts its report.

CASE REPORT

J. G., a white woman, aged 28 years, was admitted to The Sinai Hospital complaining of shortness of breath. Members of her family contributed the information that the patient had had a "cold" for several months and a cough for at least six months. According to the patient's story, she was well until four weeks before admission when she suddenly became extremely dyspneic after walking several blocks. The dyspnea was associated with aching pain in the right shoulder. From then on she had recurrent episodes of dyspnea upon exertion. About three days before admission she began to cough. Two days before admission her temperature became elevated and rose as high as 104° Fahrenheit. On occasion she had substernal pain which radiated to the right shoulder and to the right and left arms. The night before admission she expectorated blood. On the day of admission the sputum was observed to be brown. The positive findings were as follows:

Physical Examination.—The positive findings were as follows: Temperature, 102°; pulse, 140 per minute; and respirations, 32 per minute. The blood pressure was 90/74. She was obese. She was dyspneic and the mucous membranes were cyanotic. There was dullness to percussion posteriorly at the base of the right lung. Numerous râles were heard in the same area, as well as in the right upper and left lower lobes. The heart was found to be normal in size. The heart sounds were distant and the rhythm was regular. A systolic murmur was heard in the mitral area.

Laboratory Studies.—The red blood cells were 3.89 million per cubic millimeter; hemoglobin, 11.7 Gm.; and white blood cells, 23,800, of which 82 per cent were of the neutrophilic series. The blood urea nitrogen was 80 mg. per cent. The carbon dioxide combining power of the blood was 78.2 volumes per cent. Examination of the sputum failed to reveal the presence of any pneumococci. Blood for a Wassermann test was not obtained.

Course in Hospital.—The condition of the patient became rapidly worse. The blood pressure and pulse became unobtainable. Digitalis therapy was instituted, followed by sulfathiazole and adrenal cortical extract. Therapy, however, was ineffectual and the patient died less than twenty-four hours after admission. The clinical impression was bronchopneumonia. The terminal temperature was 106° Fahrenheit.

From the Laboratories of The Sinai Hospital, Baltimore, Md.
Received for publication Nov. 26, 1945.

Necropsy Findings.—The autopsy was performed almost four hours after death. The contributory findings were as follows: The heart was not enlarged and weighed 250 grams. Both ventricles were moderately dilated. The myocardium of the left ventricle was yellowish-brown with distinctly yellowish areas visible in the papillary muscles. The valve leaflets and cusps were not remarkable. Arising within the sinuses of Valsalva, corresponding to the right and left aortic cusps, there was a broad plaquelike area of thickening upon the intimal surface of the aorta which measured approximately 3 by 2 centimeters. It completely encircled and narrowed the orifice of the left main coronary artery and also encroached upon the orifice of the right main coronary artery but did not encircle it (Fig. 1). Beyond their orifices the coronary arteries were



Fig. 1.—Heart opened to show aortic valve and encroachment upon coronary artery ostia by plaque at base of aorta.

widely patent and thin-walled. The aorta contained two more plaquelike areas of somewhat smaller size in the ascending and transverse arches of the aorta. The remainder of the aorta was elastic and contained only scattered atherosclerotic streaks. There was about 200 c.c. of clear, straw-colored fluid in the right pleural cavity and 300 c.c. of a similar fluid in the left pleural cavity. The sectioned surfaces of the lungs showed extensive edema.

Fig. 2.

Fig. 3.

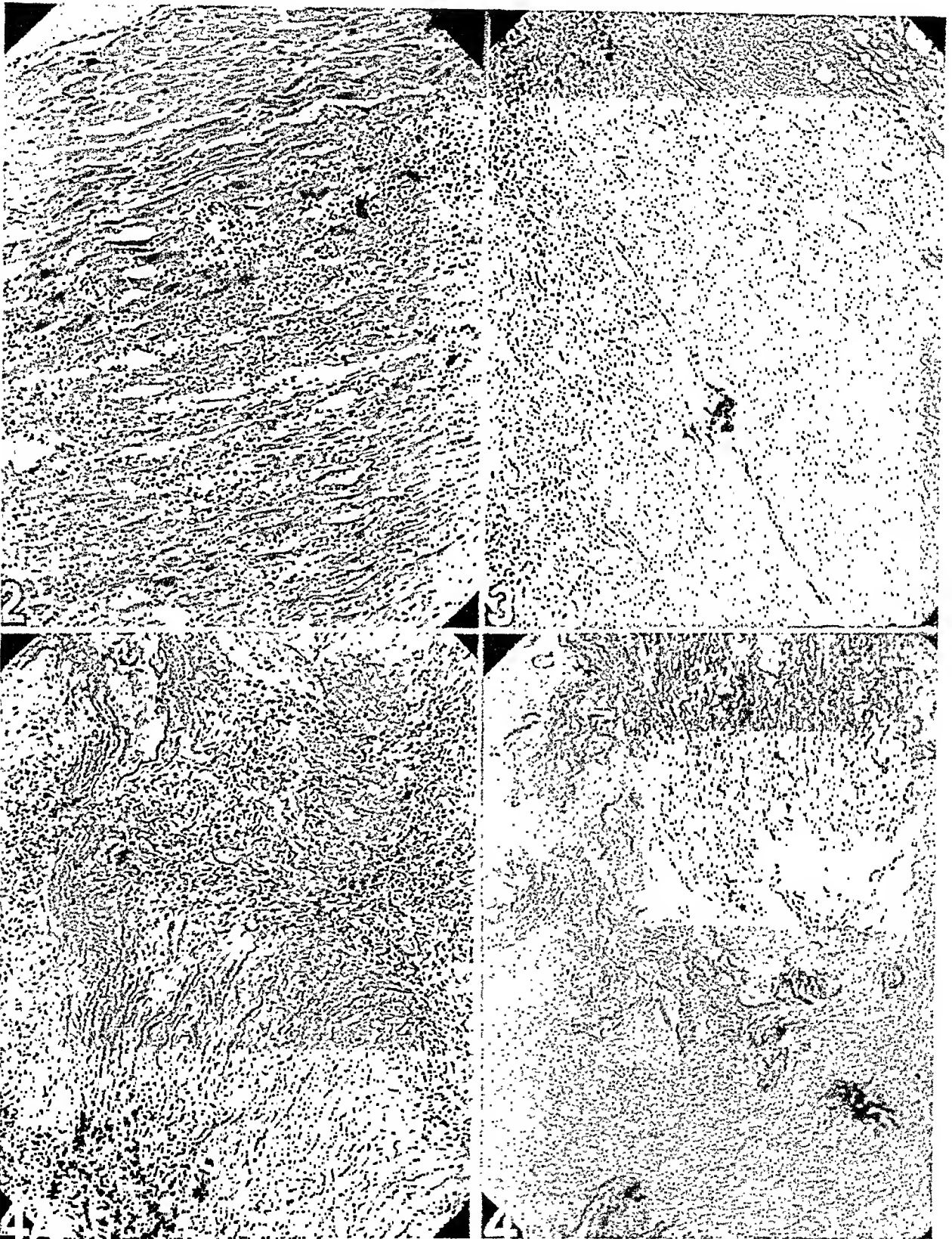


Fig. 4.

Fig. 2.—Section of myocardium of left ventricle showing infarction.

Fig. 3.—Section through plaque at base of aorta showing gummatous alteration.

Fig. 4.—A, Section of aortic plaque showing areas of medial destruction with fibrous replacement and plasma cell and lymphocytic infiltration. B, Weigert's elastica-van Gieson stain of portion of plaque in aorta showing marked destruction of the elastic tissue in the media.

Microscopic Findings.—The sections of the myocardium taken from the posterior wall as well as from the papillary muscles of the left ventricle showed tinctorial changes, loss of cross-striations, and areas of extensive necrosis with dense polymorphonuclear infiltration (Fig. 2). The sections of the large plaques observed in the aorta showed a marked intimal thickening, consisting partly of cellular and partly of collagenous connective tissue within which there were large areas of necrosis as well as fibrinoid degeneration. The areas of necrosis assumed a granular amorphous basophilic character and, in some instances, were in proximity to large collections of plasma cells and lymphocytes (Fig. 3). In some areas the media was practically completely destroyed with resulting fibrous replacement and plasma cell infiltration (Fig. 4). Many blood vessels in the media and adventitia were surrounded by collections of plasma cells and lymphocytes, and some showed a cellular intimal proliferation. The adventitia in these areas was thickened. Stains for spirochetes performed by both the Levaditi and Dieterle techniques failed to reveal their presence. Sections of the other organs merely confirmed the gross observations.

COMMENT

According to Held and Goldbloom¹ and Gordon, Parker, and Weiss,² only a few cases of gummatous aortitis have been reported in the recent literature. The first-mentioned authors claim to have found only three instances in their review of the literature. Gordon and co-authors, in a review of their own cases, found eight instances of gummatous alteration in a series of 360 cases of syphilitic aortitis.

Both Burch and Winsor³ and Love and Warner⁴ have made extensive analyses of the association of coronary ostial stenosis due to syphilitic aortitis and acute myocardial infarction. The former³ found three of a series of 185 myocardial infarctions to be due to syphilitic coronary artery ostial stenosis, and accordingly concluded that myocardial infarction as a result of syphilis is rare. In a series of 193 cases of syphilitic aortitis they found forty in which there was narrowing of the ostia of one or both coronary arteries. Of these, only three had myocardial infarction. Love and Warner⁴ analyzed their series of fifteen cases in which there was stenosis of either one or both coronary ostia. In eight of the fifteen cases there was marked fibrosis of the myocardium. In four cases there was acute myocardial infarction as evidenced by leucocytic infiltration. Corrigan,⁵ in his discussion of myocardial infarcts and syphilitic aortitis, stated that morphologic evidence was rarely demonstrated at the post-mortem examination. Von Glahn⁶ collected 687 cases of syphilitic aortitis and found among them 120 instances of occlusion or stenosis of one or both coronary artery orifices and only four infarcts of the myocardium.

Most authors emphasize the relatively early age at which syphilitic coronary artery stenosis is found. Bruenn⁶ gives the average age as 34 years. Burch and Winsor³ place the average age at 40 years. The youngest case they found was in a person 20 years of age. Gordon, Parker, and Weiss'² youngest patient with gummatous aortitis was 32 years old. Clawson⁸ reported only one case occurring in the third decade. Other authors⁵⁻⁷ report cases in patients in their thirties but none younger.

From the foregoing brief review of some of the pertinent literature on the subject, it is obvious that the present case is an instance of syphilitic aortitis

associated with coronary ostial stenosis in an individual manifesting the effects of the disease at an even earlier age than that most commonly recorded in the literature. The findings of acute myocardial infarction in our case places it in another group of relatively rare observations. The same is also true of the finding of gummatous aortitis.

The microscopic findings in our case are so characteristic that in spite of the lack of corroborative evidence in the form of a positive serologic test for syphilis or the finding of spirochetes, we feel quite certain of the etiologic character of the aortic lesion described.

SUMMARY

A case of syphilitic gummatous aortitis is reported occurring in a 28-year-old woman and associated with coronary artery ostial stenosis and acute myocardial infarction.

Attention is called to the rarity of each of the findings individually and as a group, particularly in an individual in the third decade of life.

REFERENCES

1. Held, I. W., and Goldbloom, A. A.: Cardiovascular Syphilis With Special Reference to Syphilis of the Aorta, *Urol. & Cutan. Rev.* 47: 28, 1943.
2. Gordon, W. H., Parker, F., Jr., and Weiss, S.: Gummatous Aortitis, *Arch. Int. Med.* 70: 396, 1942.
3. Burch, G. E., and Winsor, T.: Syphilitic Coronary Stenosis With Myocardial Infarction, *AM. HEART J.* 24: 740, 1942.
4. Love, W. S., Jr., and Warner, C. G.: Observations Upon Syphilis of the Heart, Coronary Ostia, and Coronary Arteries. II. With Special Reference to the Myocardial Lesions Noted in Stenosis of the Coronary Ostia, *Am. J. Syph. & Neurol.* 18: 154, 1934.
5. Corrigan, M. C.: Myocardial Infarcts and Syphilitic Aortitis, *Urol. & Cutan. Rev.* 45: 229, 1941.
6. Bruenn, H. G.: Syphilitic Disease of the Coronary Arteries, *AM. HEART J.* 9: 421, 1934.
7. Pincoffs, M. C., and Love, W. S., Jr.: Observations Upon Syphilis of the Heart, Coronary Ostia and Coronary Arteries. I. With Special Reference to the Clinical Picture Presented by Syphilitic Stenosis of the Coronary Ostia, *Am. J. Syph. & Neurol.* 18: 145, 1934.
8. Clawson, B. J.: Syphilitic Heart Disease. *Urol. & Cutan. Rev.* 45: 219, 1941.
9. Von Glahn, W. C.: Changes in the Coronary Arteries in Syphilis. From Lamb, A. B., and Turner, K. B.: Cardiovascular Syphilis, New York, 1921, Nelson Loose Leaf Living Medicine, vol. IV, p. 346. !

Abstracts and Reviews

Selected Abstracts

Lindquist, T.: Intermittent Claudication and Vascular Spasm: I. Is Vascular Spasm a Contributory Cause of Intermittent Claudication in Patients With Structural Disease of the Arteries? Acta med. Scandinav. 121:32 (I), 1945.

The author investigated the mechanism of the cutaneous pallor and coolness observed during attacks of intermittent claudication in an attempt to determine whether this represented a true vasospasm with reduction in muscle blood supply or whether it was simply the excessive effect on organically narrowed vessels of the slight cutaneous vasoconstriction that has been described in normal persons in association with exercise.

Oscillometric records were made on eight patients with intermittent claudication. The cuff was applied to the thigh or upper calf rather than the ankle since it was felt that most of the muscular branches of arteries were given off above the latter point and that measurements at the ankle might reflect changes in vessels supplying mainly skin or supporting structures. A special apparatus was used to record the relatively small pulsations of the thigh and calf.

It was found that the amplitude of pulsations decreased markedly in some patients when cramps appeared but in others the amplitude increased in a fashion similar to the normal response. The occurrence of these two types of reaction appeared to be independent of the integrity of the sympathetic supply to the limb, for both occurred in patients with and without previous lumbar sympathectomy or block.

The possibility that the diminished oscillations were due to less blood reaching the more distal muscles because it was being "stolen" by more proximal muscles was considered and rejected. It was concluded that true vasospasm did occur in some patients with intermittent claudication but not in all and that it was independent of the sympathetic innervation of the affected limb.

SÄYEN.

Griffith, G. C., and Bailey, E. T.: The Treatment of Rheumatic Fever by Roentgen Ray Irradiation. Ann. Int. Med. 24:1039 (June), 1946.

This report concerns experiences gained from irradiation therapy among 201 patients in the rheumatic fever unit at the U. S. Naval Hospital, Corona, California. All the patients had been ill with rheumatic fever which had been present for six months or more. The patients were divided into three groups. Those in the first group received 100 roentgens through the myocardium at weekly intervals for five successive weeks. Those in the second received 100 roentgens through the myocardium and over the middle and lower cervical sympathetic ganglia every week for five successive weeks. The patients in the third group received no treatment but went through the same mechanical routine as did those in Groups I and II (a lead filter was used to block out the roentgen rays). The results of this program were carefully analyzed. It was concluded that there was no greater improvement in the patients treated than in those who did not receive irradiation therapy. There was no demonstrable therapeutic value from roentgen ray therapy in the primary or in the recurrent attacks of rheumatic fever. The final conclusion is that roentgen ray therapy is not a useful procedure in the treatment of rheumatic fever.

WENDKOS.

Jones, M., and Scarisbrick, R.: The Effect of Exercise on Soldiers With Neurocirculatory Asthenia. *Psychosom. Med.* 8:188 (May-June), 1946.

The influence of effort syndrome on the reaction to exercise was studied at the Mill Hill Hospital, London, England. Effort syndrome was classified into three groups: (1) where poor physical endowment is the primary factor in producing symptoms; (2) where poor physical endowment is the primary factor in producing symptoms but the patient responds in a neurotic manner to his constitutional inferiority; (3) primarily neurotic. Since the hospital is a neurosis center, patients belonging to Group 1 were rarely seen.

Comparisons were made of the effects of exercise on thirty-five normal control subjects, twenty-five patients with effort syndrome in Group 2, and ten patients with effort syndrome in Group 3. The subjects undertook two tests: standard work, in which they pedaled a bicycle ergometer for five minutes, and maximal work, in which they pedaled to the point of exhaustion in ten minutes. Observations were made on the pulse rate and blood lactate level.

The patients with effort syndrome in Group 2 (constitutional) showed a mean blood lactate rise of 28.9 mg. per cent after standard exercise. The corresponding figure for the normal controls was 21.1 mg. per cent. The patients in Group 3 (psychogenically produced effort syndrome) showed a blood lactate rise similar to that of those in the control group. The pulse rate response to standard work was a greater rise and a slower decrement in those in the effort syndrome group than in those in the control group. Group 2 patients had a higher rise and a slower decrement than did the Group 3 patients.

After maximal work, the mean blood lactate rise for the control group was 78.0 mg. per cent and for the patients with effort syndrome, 50.2 mg. per cent. The mean lactate rise was essentially similar for the patients with effort syndrome in both Groups 2 and 3. The pulse rate response to maximal work, in contrast to the effect of standard work, was similar in both patients and normal controls.

It appeared from these observations that a satisfactory differentiation between Group 2 (constitutional) and Group 3 (psychogenically produced) effort syndrome can be made on the basis of the blood lactate response to standard exercise. When maximal exercise is used, it is evident that patients with effort syndrome, unlike the normal controls, give up exhausting physical work before a "physiological" end point is reached, due to what amounts to effort phobia.

LAPLACE.

Westermarck, N.: A Method for Determining the Blood Pressure in the Pulmonary Artery. *Acta. Radiol.* 26:302 (No. 3), 1946.

By making multiple roentgenograms of the chest in subjects performing a modified Valsalva experiment by blowing into a closed system in which pressure was measured, a point was found at which a marked diminution in the diameter of the pulmonary vascular shadows appeared. In twenty normal subjects this phenomenon occurred at a pressure of 25 to 30 mm. of mercury. This was believed to approximate closely the systolic pressure in the pulmonary arterial system. Ninety patients with mitral stenosis were studied in a similar manner. Twenty-two of these had clinical signs of a mild valvular lesion and showed pressures within the normal range. In thirty patients with moderate mitral stenosis the pressures ranged from 30 to 60 mm. of mercury, while thirty-eight with severe mitral stenosis required a pressure of over 60 mm. of mercury to produce significant decreases in the size of their pulmonary vascular shadows. It is believed that this method is a satisfactory nonsurgical procedure for determining pulmonary blood pressures in man.

SÄYEN.

Pereira, A. de Sousa.: The Innervation of the Veins: Its Role in Pain, Venospasm and Collateral Circulation. *Surgery* 19:731 (May), 1946.

The nerve supply to the veins contains afferent sensory pathways in addition to the efferent vasomotor components. Mechanical or chemical stimulation of the veins causes pain. The relief of venous pain and venospasm in acute phlebitis and thrombophlebitis by the injection of 1

per cent novocain into the affected vein, or by the anesthetic block of the sympathetic chain, lasts for a longer period than the anesthetic action of the drug can account for. This suggests that venospasm may play an important role in the mechanism of pain. Venography in the author's cases demonstrated that venospasm extended far beyond the phlebotic or thrombosed vein. This venospasm may be relieved by peripheral anesthesia of the venous wall or by interruption of the efferent pathways of the sympathetic chain.

In cases of thrombophlebitis it was observed that repeated anesthetic blocks of the sympathetic chain with procaine hydrochloride, perivenous sympathectomy, or resection of the regional sympathetic chain was followed by an increase in collateral venous circulation. These investigations have demonstrated that physiologic or anatomic interruption of the innervation of the veins may relieve the pain and the venospasm and also increases the development of collateral circulation. The facts observed suggest that the plan of the innervation of the veins in relation to pain, spasm, and collateral circulation is similar to that of the afferent sensory and the efferent vasomotor pathways of the arteries.

NAIDE.

Guthrie, D., and Gagnon, G.: The Prevention and Treatment of Post-Operative Lymphedema of the Arm. *Ann. Surg.* 123:925 (May), 1946.

The most important factor in prevention of lymphedema of the arm following radical mastectomy is the avoidance of infection. Prolonged immobilization of the arm following the operation should be condemned. Absolute free and early mobilization should be instituted. It is as important to mobilize the arm following radical mastectomy to prevent edema as it is to exercise the legs for prevention of phlebothrombosis and thrombophlebitis following operation in the pelvis. The patient is requested to move her arm as soon as she reacts from the anesthesia. If roentgenotherapy is indicated, one should avoid a destructive type of dermatitis.

The authors recommend treatment of post-operative lymphedema by the Beck operation. Five strips of celloidin are inserted into the subcutaneous tissue and left in place for three weeks. This procedure aids in the development of collateral channels. The Kondoleon operation has proved to be of no value.

NAIDE.

Stead, E. A., Jr., Brannon, E. S., and Brannon, A. J.: Concentrated Human Albumin in the Treatment of Shock. *Arch. Int. Med.* 77:564 (May), 1946.

Tests of the usefulness of human albumin as substitutes for plasma have been made by observing the effects of giving it intravenously to seven normal subjects and thirty-four patients with circulatory failure. The following studies were made on these subjects: mean atrial pressure, oxygen consumption, optical recording of arterial pressure, oxygen content of arterial and right atrial blood, cardiac output, plasma volume, and hematocrit.

No untoward effects were noted. None of the patients experienced chills, fever, urticaria, pulmonary edema, or circulatory collapse.

Seven normal subjects received 1 liter of a 5 per cent solution of human albumin intravenously within a period of fifteen to thirty-one minutes. Two consistent changes were noted. The atrial pressure always rose and the hematocrit reading and concentration of hemoglobin always fell. The arterial pressure, cardiac rate, consumption of oxygen, and arteriovenous oxygen difference showed no consistent change.

Studies were also made on thirteen patients with circulatory insufficiency following acute hemorrhage, on seven additional patients following injuries to the chest, and on two patients with hemopericardium resulting from penetrating wounds. All but two of these patients received 50 Gm. of a 25 per cent solution of human albumin. The results of therapy in patients with hemorrhage were uniformly good. The results of therapy in the patients with burns, dehydration, and infection were satisfactory.

The average increase of plasma volume produced by 1 Gm. of albumin was 14 cc. Although albumin is not as useful in the treatment of shock as is whole blood, albumin is nevertheless an extremely useful substitute for plasma. From the standpoint of speed and convenience of ad-

ministration, convenient packaging, small bulk, stability under varying temperatures, and absence of bacterial contamination, concentrated albumin is ideal. In civilian practice where whole blood and plasma are readily available, albumin may not be used extensively in the treatment of shock. Under the conditions of war, concentrated albumin has many advantages.

BELLET.

Flett, D. M., and Powell, W. N.: Acute Bacterial Endarteritis. J.A.M.A. 131:397 (June 1), 1946.

These authors present what they consider to be the first report of endarteritis of the ductus due to *Diplococcus pneumoniae*. This infection was arrested on the thirteenth day after a total of 3,875,000 units of penicillin had been given within a period of twenty-eight days. At a later date, the patent ductus was ligated. Six months after the original observation the patient had gained 25 pounds in weight and the auscultatory phenomena previously observed were no longer present. The patient was apparently well ten months after the original period of treatment.

BELLET.

Segers, M.: A Study of the Gaskell Effect. Arch. internat. de pharmacodyn. et de therap. 71:173 (Nov.), 1945.

One of the most typical actions of the vagus nerve on the heart is that of producing positive variations of polarization, known as the Gaskell effect. In order to determine the factors involved in this phenomenon, a study was made of the action of acetylcholine on the electrical charges on the surface of the myocardium of the frog: in the rhythmically beating heart the positive potentials are due to the disappearance of late negative potentials; in the nonbeating heart, acetylcholine does not produce any positive variation. The Gaskell effect results, therefore, not from a modification of the current of demarcation of the myocardium, but from a modification of the evanescent state of polarization represented by the after-potentials. The action of adrenalin is identical but is opposite in direction.

The Gaskell effect is often regarded as the factor responsible for the inhibitory action of the vagus. This view is acceptable but it must be understood that the mechanism is not the only one involved since the cardio-moderator effects of the vagus can occur in the absence of any variation of polarization.

The late negativity of the heart is accompanied by a postsystolic contracture occupying the interval which separates the beats. Under the influence of acetylcholine, the postsystolic contracture disappears at the same time as the late negativity. Acetylcholine does not, however, produce any change in tonus in the resting heart.

The after-potentials demonstrate the existence of a state of supernormality produced by the heart beats and suppressed by acetylcholine. The Gaskell effect corresponds, therefore, to suppression of a state of excitation and not to a true inhibition of the heart.

LAPLACE.

Wallace, L., Katz, L. N., Langendorf, R., and Buxbaum, H.: Electrocardiogram in Toxemias of Pregnancy. Arch. Int. Med. 77:405 (April), 1946.

The authors discuss the presence of electrocardiographic changes during toxemias of pregnancy. Their series included twelve cases of toxemia of pregnancy without eclampsia. Group I consisted of two patients who developed acute left ventricular failure at the time of labor. Group II was made up of four patients who manifested no heart failure but presented electrocardiographic changes. Group III consisted of six patients in whom there was no evidence of heart failure and in whom no electrocardiographic abnormalities were observed despite the presence of toxemia.

In Group I, electrocardiographic changes were observed which were characterized by inverted T waves in Leads I, CF_2 , and CF_4 and by the absence of any pronounced S-T deviation or changes in the QRS complex. In one of the patients, complete restitution to normal occurred within

fifteen weeks; the other could not be followed. The authors suggest that the changes observed in patients with toxemia who experienced cardiac failure simulate rather closely the changes occasionally seen in acute nephritis.

In Group II, during the last trimester of pregnancy, inversion of the T wave in CF_2 and CF_4 was present; this reverted to normal within one week following delivery. Similar findings were occasionally observed in normal persons as well as in patients with toxemia of pregnancy.

The possible causes of these electrocardiographic abnormalities are discussed.

BELLET.

Merrill, A. J.: Edema and Decreased Renal Blood Flow in Patients With Chronic Congestive Heart Failure: Evidence of "Forward Failure" as the Primary Cause of Edema. J. Clin. Investigation 25:389 (May), 1946.

In patients with chronic congestive heart failure the cardiac index (liters per square meter per minute) tends to be lower than average normal. These patients also exhibit a reduction in renal plasma flow, glomerular filtration rate, and sodium clearance.

Renal venous congestion is not responsible for the reduced renal plasma flow because no correlation is found to exist between the level of venous pressure and the volume flow of blood through the kidneys. On the other hand, a significant correlation is found between renal plasma flow and the cardiac index; that is, when cardiac output is reduced, renal plasma flow is reduced (frequently to a greater extent than the cardiac output). Associated with the reduction in renal plasma flow is a significant decrease in sodium clearance which is accounted for chiefly by a low filtration rate rather than by increased tubular reabsorption of sodium. Sodium retention then leads to edema formation.

The data indicate that "forward" rather than "backward" failure is the cause of edema formation in chronic congestive heart failure despite the fact that many patients have cardiac indexes which fall well within the normal range. This apparent discrepancy is explained by suggesting that no absolute level of cardiac output exists below which patients develop cardiac failure: the patient with thyrotoxicosis may have a normal or increased cardiac index and still develop congestive heart failure if the cardiac index fails to meet metabolic demands.

FRIEDLAND.

Zeek, P. M.: Heart Weight: II. The Effect of Tuberculosis on Heart Weight. Arch. Path. 41:526 (May), 1946.

The author points out that emaciation in tuberculous patients and not tuberculosis per se is the important factor for the common finding of a small heart. In the presence of a well-maintained nutrition, a tuberculous patient should have a heart of normal weight.

GOULEY.

Postoloff, A. V., and Cannon, W.: Genesis of Aortic Perforation Secondary to Carcinoma of the Esophagus. Arch. Path. 41:533 (May), 1946.

To the total series of sixty cases reported to date, the authors add two of their own cases of perforation of the aorta by carcinoma of the esophagus. In both of these women, aged 76 and 38 years, respectively, there was a history of progressive dysphagia and sudden death preceded by hemorrhage from the nose and mouth.

Necropsy revealed that the wall of the aorta had become undermined, leading to small intimal perforations, not because of actual tumor cell invasion of the media and intima, but as a result of cellular infiltration of the vaso vasorum with secondary thrombosis and fibroblastic reaction in the vessels.

GOULEY

Wexler, J., Whittenberger, J. L., and Himmelfarb, S.: An Objective Method for Determining Circulation Time From Pulmonary to Systemic Capillaries by the Use of the Oximeter. J. Clin. Investigation 25:447 (May), 1946.

The oximeter is an instrument which measures continuously the oxygen saturation of arterial blood by means of photoelectric colorimetry of the intact fully flushed ear. The interval between the beginning of a deep breath of 100 per cent nitrogen and the beginning of the downward deflection of the recording device (a galvanometer) was considered to be the time required for the unsaturated blood to pass from the lungs to the ear. In thirty-five subjects without heart disease the range of values was 4.1 to 7.0 seconds with an average value of 5.2 seconds. Twenty-three subjects (66 per cent) were within the range of 4.6 to 5.5 seconds and the variation on repeated tests in any individual did not exceed 1.8 seconds. Of course the recorded values are probably higher than the true pulmonary to systemic capillary circulation time since the measurement includes the time of inspiration, diffusion time of the nitrogen in the residual air, the galvanometer lag, and the reaction time of the observer. The method promises to be useful and accurate in that it is objective, requires a minimum of cooperation on the part of the patient, and eliminates the variable arm-to-lung segment in the usual method of measuring the circulation time.

FRIEDLAND.

Heymans, C., and Capet, L.: The Influence of Magnesium and Calcium on the Proprioceptive Regulation of Arterial Pressure. Arch. internat. de pharmacodyn. et de thérap. 51:164 (Nov.), 1945.

It is well known that magnesium has a depressant action on the central nervous system which can be neutralized by calcium. On the other hand, calcium deficiency has been shown to cause a diminution of the aortic and carotid sinus reflexes which control the proprioceptive regulation of arterial pressure. An investigation was therefore made of the reciprocal influences of magnesium and calcium on the vasomotor reflexes originating in the carotid sinus and of the action of calcium on arterial hypertension produced by suppression of the four aortic and carotid sinus nerves. The studies were performed on dogs and led to the following conclusions:

1. Magnesium sulphate can depress and almost paralyze the vasomotor reflexes concerned in the proprioceptive regulation of general arterial pressure.
2. Calcium chloride or thiosulphate can re-establish the vasomotor reflexes of the carotid sinus which have been depressed or paralyzed by magnesium.
3. Suppression of the four depressor nerves produces a substantial hypertension which may be permanent or transient. The fall of arterial pressure after hypertension is produced by suppression of the depressor nerves is due to cardiovascular collapse caused by the hypertension.
4. Calcium administered intravenously protects the heart against the effects of sudden hypertension produced by suppression of the four depressor nerves.
5. Calcium administered intravenously, on the one hand, stimulates the heart but, on the other hand, increases and maintains the hypertension produced by suppression of the depressor nerves.

LAPLACE.

Book Reviews

PHONOCARDIOGRAPHIE, AUSCULTATION COLLECTIVE (ACOUSTIQUE—TECHNIQUE—CLINIQUE). By C. Lian, G. Minot, and J. J. Welti. Paris, 1941, Masson & Cie, 253 pages.

This monograph on phonocardiography represents years of work on this subject by the authors. It is complete in scope and quite extensive in detail. In the first place, there is a discussion of principles of physics involved in the recording and interpretation of heart sounds; this is followed by a detailed description of the various apparatus used in making their studies of heart sounds, venous pulse, and apex impulse. They have been able to record simultaneously the electrocardiogram, the phonocardiogram, the venous pulse tracing, and the electrokymogram or tracing of the apex impulse. Further, in the mechanical domain, they have developed a good method for recording heart sounds on phonograph records and for their rendition over a loud speaker for the benefit of group auscultation. In addition to the studies on cardiology, they present a chapter on recording of vascular murmurs and another chapter on the recording of sound tracings of respiration and of abdominal ascitic waves produced by percussion.

For students of cardiology this monograph will serve as a work of reference and as an important painstaking contribution to the special literature of the subject of phonocardiography. The chapters on doubling of the first and second sounds, on the third sound, and on gallops are well written and well illustrated with many figures.

WILLIAM C. KUZELL, M.D.

THE VENOUS PULSE AND ITS GRAPHIC RECORDING. By Franz M. Groedel, M.D. New York, N. Y., 1946, Brooklyn Medical Press, Inc., 223 pages.

This book describes the author's experience in recording the venous pulse and his views on interpretation of the usual waves as well as a number of additional waves which appear in his records. There is also a section on the pneumo-cardiogram and the esophagocardiogram. The illustrations are good.

J. K. LEWIS, M.D.

ELECTROCARDIOGRAPHY IN PRACTICE. By Ashton Graybiel, M.D., and Paul D. White, M.D., with the assistance of Louise Wheeler, A.M., and Conger Williams, M.D. Second edition. Philadelphia and London, 1946, W. B. Saunders Company, 458 pages, 323 illustrations. Price \$7.00.

This useful book has been expanded and much new material has been added. The original format and plan have been retained with the presentation of the clinical information and electrocardiographic interpretations on one page and the electrocardiograms shown on the facing page. Over fifty figures have been added to this new edition and more attention is directed to the pre-excitation electrocardiogram. Some consideration is given also to the more fundamental aspects of electrocardiography. New charts have been included which summarize in tabular form the characteristics of the various arrhythmias, the electrocardiographic findings in various types of heart disease and condition secondarily affecting the heart, and the electrocardiographic effects of many drugs and physiological processes. The valuable and instructive section of the book containing "test electrocardiograms" is made up entirely of new material.

As in the first edition of the work, "coronary heart disease" is given as an etiological diagnosis for many of the electrocardiographic deviations discussed. Although it is agreed that coronary arterial disease is accountable for the majority of these abnormalities, this usage may incline some readers to the usually unjustified practice of making pathological diagnoses such as this from electrocardiographic data alone in the absence of such extensive clinical information as is available with these cases. Doctors Graybiel and White state that they have found a lead from the right sternal margin (precordial position 1) rarely useful. This experience is not in accord with that of other observers who have been interested in multiple precordial leads and may account for the lack of emphasis in this volume upon the contrast in form of the precordial electrocardiogram in right and left ventricular hypertrophy. The atlas system of presentation makes for some repetition of discussion. While this may serve a useful teaching purpose, it may be disadvantageous when unintended inconsistencies occur. For example, in an early section of the book, it is said that the records under consideration display both complete atrioventricular block and bundle branch block, whereas at a later point, the writers amplify the discussion to indicate correctly that these diagnoses cannot be made together because of uncertainty regarding the site of the idioventricular pacemaker. The illustrations are very clear and well presented, although Fig. 89, page 119, is inverted and reversed. The typography and paper are of good quality.

This book should serve well as an aid in the interpretation of electrocardiograms as they are met in general practice, the purpose for which it was written. It should be particularly valuable in that it provides a larger number of quite typical electrocardiograms for study and review.

FRANCIS F. ROSENBAUM.

American Heart Association, Inc.

1790 BROADWAY AT 58TH STREET, NEW YORK, N. Y.

DR. ROY W. SCOTT
President

DR. HOWARD F. WEST
Vice-President

DR. GEORGE R. HERRMANN
Treasurer

DR. HOWARD B. SPRAGUE
Secretary

BOARD OF DIRECTORS

DR. EDGAR V. ALLEN..... Rochester, Minn.
DR. GRAHAM ASHER..... Kansas City, Mo.
*DR. ARLIE R. BARNES..... Rochester, Minn.
DR. ALFRED BLALOCK..... Baltimore
*DR. WILLIAM H. BUNN..... Youngstown, Ohio
DR. CLARENCE DE LA CHAPELLE..... New York City
*DR. TINSLEY R. HARRISON..... Dallas
DR. GEORGE R. HERRMANN..... Galveston
DR. T. DUCKETT JONES..... Boston
DR. LOUIS N. KATZ..... Chicago
DR. SAMUEL A. LEVINE..... Boston
DR. GILBERT MAFOUARDI..... Chicago
*DR. H. M. MARVIN..... New Haven
*DR. EDWIN P. MAYNARD, JR..... Brooklyn
*DR. THOMAS M. McMILLAN..... Philadelphia
DR. JONATHAN MEAKINS..... Montreal, Can.
DR. E. STERLING NICHOL..... Miami

DR. HAROLD E. B. PARDEE..... New York City
DR. WILLIAM B. PORTER..... Richmond, Va.
*DR. DAVID D. RUTSTEIN..... New York City
*DR. JOHN J. SAMPSON..... San Francisco
DR. ROY W. SCOTT..... Cleveland
*DR. HOWARD B. SPRAGUE..... Boston
DR. GEORGE F. STRONG..... Vancouver, B. C., Can.
DR. WILLIAM D. STROUD..... Philadelphia
DR. HOMER F. SWIFT..... New York City
DR. WILLIAM P. THOMPSON..... Los Angeles
DR. HARRY E. UNGERLEIDER..... New York City
*DR. HOWARD F. WEST..... Los Angeles
DR. PAUL D. WHITE..... Boston
DR. FRANK N. WILSON..... Ann Arbor
*DR. IRVING S. WRIGHT..... New York City
DR. WALLACE M. YATER..... Washington, D. C.

*Executive Committee.

DR. H. M. MARVIN, *Acting Executive Secretary*

ANNA S. WRIGHT, *Office Secretary*

Telephone, Circle 5-8000

THE American Heart Association is the only national organization devoted to educational work relating to diseases of the heart. Its activities are under the control and guidance of a Board of Directors composed of thirty-three eminent physicians who represent every portion of the country.

A central office is maintained for the coordination and distribution of important information. From it there issues a steady stream of books, pamphlets, charts, films, lantern slides, and similar educational material concerned with the recognition, prevention, or treatment of diseases of the heart, which are now the leading cause of death in the United States. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning the circulation of blood and lymph. Any physician or investigator may become a member of the section after election to the American Heart Association and payment of dues to that organization.

The income from membership and donations provides the sole financial support of the Association. Lack of adequate funds seriously hampers more intensive educational activity and the support of important investigative work.

Annual membership is \$5.00. Journal membership at \$11.00 includes a year's subscription to the AMERICAN HEART JOURNAL (January-December) and annual membership in the Association. The Journal alone is \$10.00 per year.

The Association earnestly solicits your support and suggestions for its work. Membership application blanks will be sent on request. Donations will be gratefully received and promptly acknowledged.

American Heart Journal

VOL. 32

DECEMBER, 1946

No. 6

THE EXPANDED PROGRAM OF THE AMERICAN HEART ASSOCIATION FOR 1947

NATIONAL HEART WEEK, FEBRUARY 9, 1947

THE current activities of the American Heart Association are of national interest to physicians as well as to laymen who have long looked for the development of a comprehensive public health program directed against diseases of the heart and blood vessels—the leading cause of death in the United States.

Those familiar with its growth will recall that the American Heart Association was founded in 1924 to combat the growing prevalence of heart disease. During the following two decades, the American Heart Association developed professional prestige and acceptance as the only national agency devoted to educational work relating to diseases of the heart. Organized primarily as a professional scientific organization, the Association concerned itself largely with the publication of the *American Heart Journal*, the only journal published in the United States which limits itself to problems of the heart and blood vessels; with the preparation of other materials for the postgraduate education of physicians; and with the establishment of standards in the field of cardiovascular disease.

The war stimulated the development of special activities particularly with reference to rheumatic fever. In 1944, recognizing the crucial need for a national program to fight rheumatic fever and rheumatic heart disease, the American Heart Association called a conference to consider the organization of a program. The conference was attended by representatives of practically all national voluntary health organizations and governmental agencies concerned with rheumatic fever and by representatives of the Army, Navy, U. S. Public Health Service, the Veteran's Administration, and the Children's Bureau.

Following this conference, the American Council on Rheumatic Fever of the American Heart Association was formed with representatives of twelve national medical agencies.* Today the Council is concerned with all phases of the American Heart Association's program which relate specifically to rheumatic fever. It operates administratively through the American Heart Association.

Earlier this year, the American Heart Association reorganized its administrative structure and broadened its objectives in order to meet the urgent need for national action in solving the medical, social, and economic problems of heart disease. Prominent laymen were admitted to membership on the various executive boards, and a program of interrelated membership with all local Heart Associations was instituted. In order to preserve the scientific aspects of the program of the American Heart Association, a Scientific Council, composed of representatives of all scientific fields contributing to our knowledge of heart disease, is being formed.

*American Academy of Pediatrics, American Association of Medical Social Workers, American College of Physicians, American Heart Association, Inc., American Hospital Association, American Medical Association, American Nurses' Association, American Public Health Association, American Rheumatism Association, American School Health Association, National Organization for Public Health Nursing, and National Society for Crippled Children and Adults.

The extent to which the American Heart Association has expanded its objectives is indicated in this condensed outline of its 1946-1947 program.† This program calls for the functioning of the American Heart Association as a clearing house for cardiovascular activities throughout the United States; for a national informational campaign to educate the public on essential problems of heart disease; for postgraduate education of the medical profession, including medical students, in cardiac and vascular diseases; for provision for the application of public health techniques to control rheumatic fever and other heart diseases through the establishment of standards for the many facilities needed in such programs, the stimulation of more accurate vital statistics, and the application of epidemiologic techniques to the study of heart disease and rheumatic fever; for the health education of other professional groups including social workers, teachers, school administrators, physical education instructors, school physicians, public health nurses, and public health workers; for aid to the cardiac patient in employment; for re-evaluation of cardiac disability in life, health, and accident insurance; and for sponsoring and financing clinical and laboratory research.

The recent award of \$50,000 by the American Legion to the American Council on Rheumatic Fever of the American Heart Association has done much to initiate an important approach to rheumatic fever. One-half of this amount has been allotted to the creation of two three-year research fellowships. Twelve thousand five hundred dollars have gone to the establishment of a Statistician's Office which is providing a much-needed statistical service for planning community rheumatic fever registries and the preparation of satisfactory methods for the classification of deaths from heart diseases. The remainder of this grant is being spent for the first of a series of medical field consultants to work directly with communities requiring aid in setting up rheumatic fever programs.

The American Legion's grant illustrates the need of the American Heart Association and its affiliate, the American Council on Rheumatic Fever, for voluntary financial support in order to undertake the various activities outlined in its program. The 1947 budget of the Association requires a minimum of \$286,000 for administration. Grants in aid for research projects call for an additional budget of \$275,000. This total budget of \$561,000, which has been approved by the National Budget Committee, represents the minimum goal required by the American Heart Association to carry forward its program and, at the same time, to create the basis for a national public fund-raising drive in 1948.

To provide the necessary public acceptance for such a drive, the American Heart Association is now conducting a nationwide program of public information and education on diseases of the heart and blood vessels. The public is being informed of the significance of high blood pressure, infections, overweight, rheumatic fever, and other factors contributing to various types of heart disease.

Plans have been developed for the observance of National Heart Week which is to be inaugurated Feb. 9, 1947. During this week, the importance of care, treatment, prevention, and study of circulatory problems will be emphasized, and the public will be reminded that heart disease is our *first* national health problem and that it can be combatted only with the fullest cooperation of the scientific worker, the specialist in heart and peripheral vascular diseases, the practicing physician, and the individual citizen and his community.

It is the plan of the American Heart Association to carry out selective fund-raising activities during National Heart Week and during the remainder of the year in cooperation with local Heart Associations where they exist. As the public becomes informed and aware of the significance of heart disease as a serious public health problem, the stage will be set for a comprehensive nationwide appeal for contributions in 1948.

†Those interested in securing a more detailed discussion of this program are requested to write to the American Heart Association, Inc., 1700 Broadway, New York, N. Y.

Original Communications

THE ESOPHAGEAL ELECTROCARDIOGRAM IN ARRHYTHMIAS AND TACHYCARDIAS

SCOTT BUTTERWORTH, M.D., AND CHARLES A. POINDEXTER, M.D.
NEW YORK, N. Y.

THE technique of taking electrocardiographic tracings with an electrode in the esophagus is a procedure which dates from the early days of electrocardiographic research.^{*} Special studies¹⁻⁷ have demonstrated the use of these leads in a variety of conditions. The present paper deals only with the value of the esophageal electrocardiogram in certain arrhythmias and tachycardias, although it is also of recognized value in the study of the electrical field of the heart and in the diagnosis of posterior myocardial infarction.

There is nothing new or unique in this work, but for some time we have been impressed that certain electrocardiograms are difficult or impossible of accurate interpretation without absolute knowledge of the position of the P wave. All too often, both in published and unpublished reports, the interpretation has been based upon theory rather than on demonstrated fact, and it has seemed to us that in selected cases valuable additional information could be obtained by the use of the esophageal lead. For this reason, it has been our practice to take esophageal electrocardiograms in all cases where the P waves were not distinctly visible in any of the leads from the surface of the body. Occasionally the P waves may be augmented by paired leads from the right sternal border, but the most satisfactory lead for demonstration of P waves is derived from an electrode in the esophagus adjacent to the auricles. An electrode in this area produces a pattern approaching that obtained by a direct lead from the surface of the auricle.

Esophageal electrodes may be simple, having a single terminal at the tip of the tube, or they may be complex, having numerous terminals located at intervals near the tip. For all practical purposes, a single terminal is very satisfactory, and such a device may be constructed with a few minutes of labor. An ordinary Rehfuess stomach tube is cut to a length of about 70 centimeters. A small bolt which will conveniently fit the diameter of the tube is soldered to a fine copper wire (about No. 34). A globule of solder is attached to the head of the bolt to provide a round, smooth tip which acts as the contact with the wall of the esophagus. The wire is then inserted through the tube and connected to a terminal at the opposite end so that the wire is fairly taut in the tube. We have found that a terminal from the base of an old radio tube is very useful for this purpose. The tube is then marked in centimeters from the tip to the 55 cm.

From the Division of Cardiology, Department of Medicine, New York Post-Graduate Medical School and Hospital, Columbia University.
Received for publication April 30, 1946.

level with black lacquer. Care must be taken in cleaning the tube after use to avoid stretching the tube, for this may break the fine wire or one of the connections.

The technique of inserting the tube is exactly the same as for any stomach tube. We generally insert the tip through a nostril with the patient in the sitting position and push it into the esophagus during the act of deglutition as the patient drinks water. Most patients tolerate this procedure well and it is only occasionally necessary to anesthetize the pharynx. A small portion of electrode paste is rubbed on the tip just before insertion. After the tube is inserted to the 55 cm. level, the patient is placed in a supine position for the recording of the electrocardiogram. The esophageal lead can be paired with any other lead but we commonly use the left leg or preferably the indifferent electrode of Wilson.

Occasionally there is poor electrical contact with the esophagus after the tube is in place; this can often be improved by having the patient drink some warm saline solution. Another difficulty which produces artefacts in the record is sliding of the electrode on the mucous membrane of the esophagus with each beat of the heart. This produces very bizarre complexes but can usually be obviated by shifting the position of the electrode slightly.

At the 55 cm. level the tip of the tube is usually in the stomach. A record is taken at this level and the tube is then withdrawn in increments of 2.0 or 2.5 cm. to the 30 cm. level, which usually places the tip above the heart. Levels from 55 to 40 cm. are usually in close proximity to the diaphragmatic surface of the heart and accentuate the ventricular potentials, while those from the 40 to the 30 cm. levels usually overlie the auricles and accentuate the auricular potentials. At the lower levels one often encounters difficulty in keeping the string in the field due to respiratory movement of the diaphragm. This can usually be controlled by instructing the patient to suspend respiration temporarily at the end of a normal expiration. The amplifying types of electrocardiographic machines are somewhat easier to use in that the beam balances and stays in the field more easily, but all instruments are satisfactory and we have made many records on both string and amplifying instruments.

As a general rule, the following types of mechanisms offer difficulty in interpretation and may be inaccurately diagnosed due to inability to identify the P wave definitely:

1. Electrocardiograms in which the P wave is superimposed on the QRS complex or the T wave.
2. Electrocardiograms in which the voltage of the P wave is too low to permit positive identification.
3. Tachycardia of either supraventricular or ventricular origin in which P waves cannot be definitely identified.

The following examples are presented to illustrate these points.

ILLUSTRATIVE ELECTROCARDIOGRAMS

The first case (Fig. 1) is an illustration of a P wave buried in the T wave. Esophageal leads are not usually necessary in this type of case for the P-R

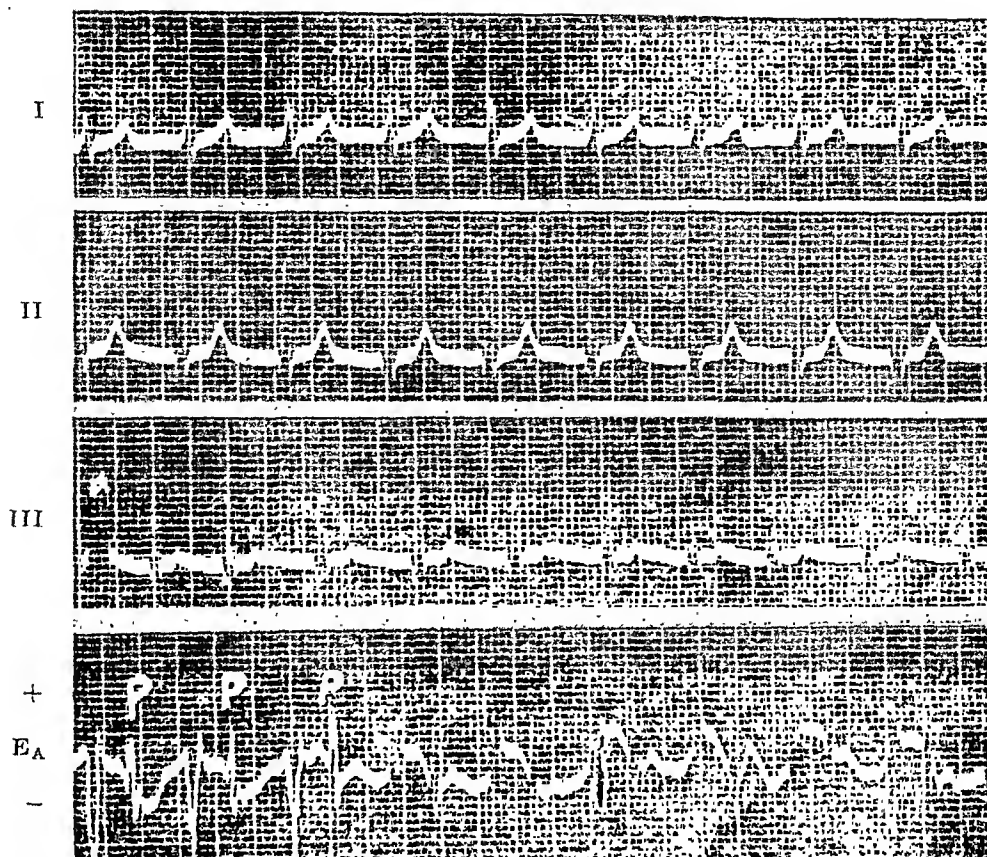


Fig. 1.—The standard leads in this case do not show definite P waves, but from the auricular level of the esophagus the P waves are seen to fall on the summit of the T waves. (The first three complexes of the lead from the auricular level of the esophagus (E_A) have been retouched to improve reproduction, and the P waves are marked.)

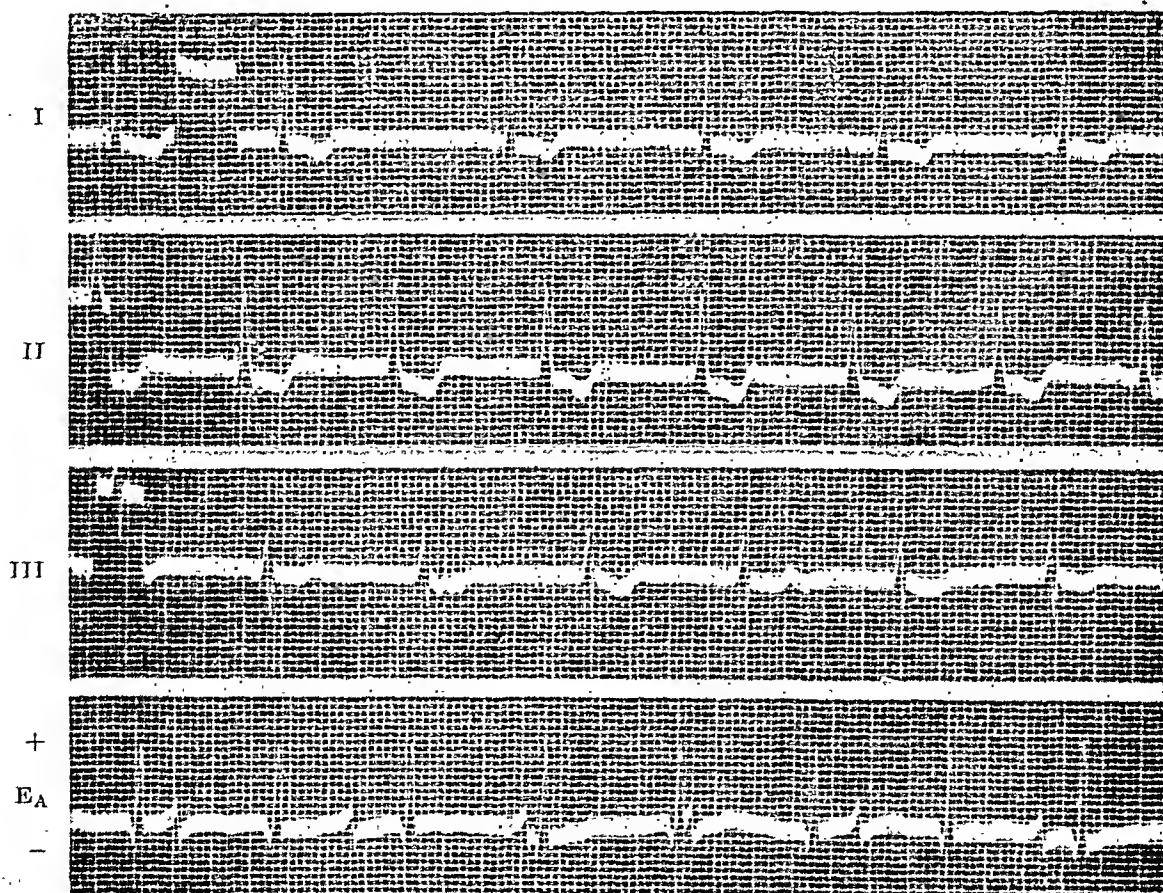


Fig. 2.—Electrocardiogram illustrating extremely low voltage of the P waves in the standard leads. The E_A lead clearly shows the P waves. There is complete dissociation between the auricles and ventricles.

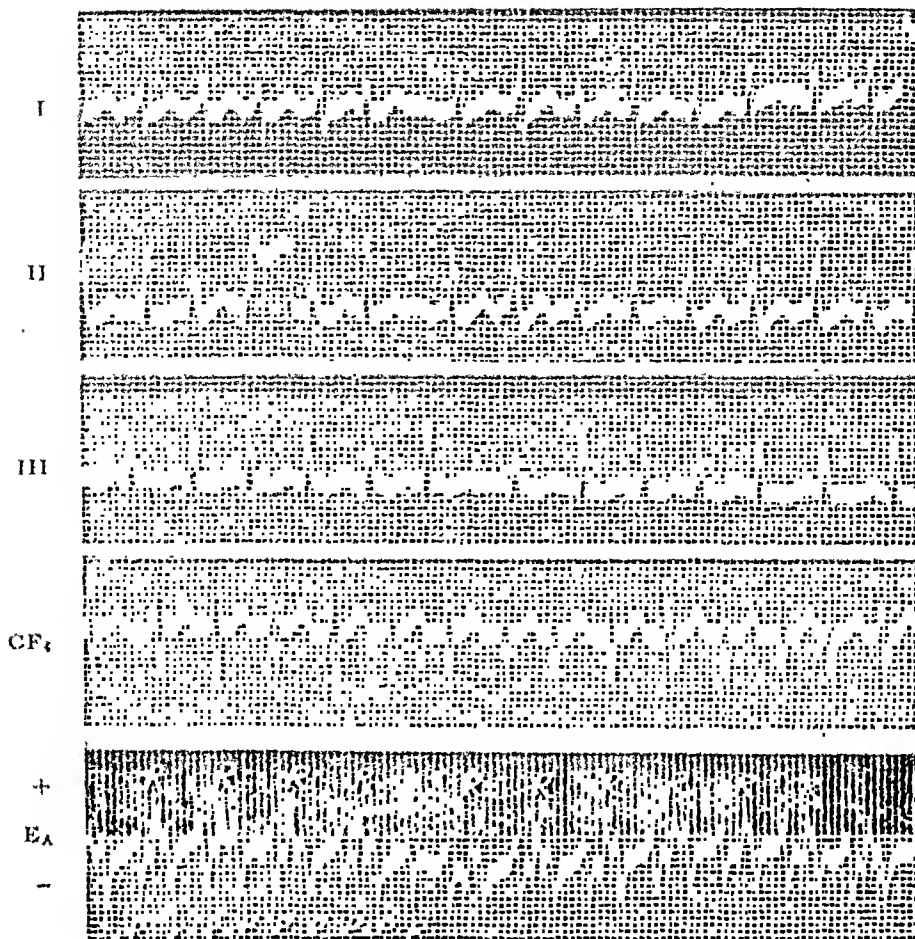


Fig. 3.

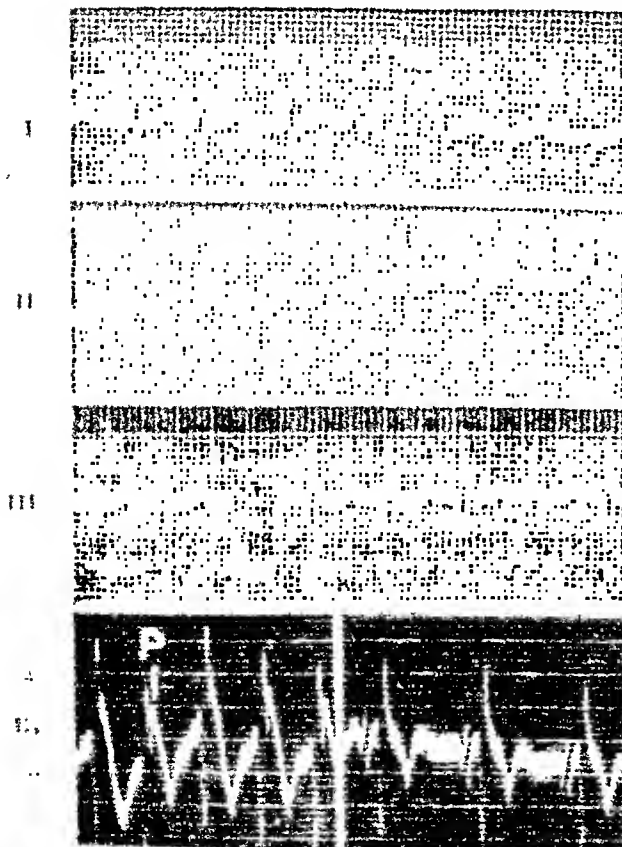


Fig. 4.

Fig. 3.—The standard leads reveal no definite P waves and an irregular rhythm. The supposition would be that one is dealing with rapid auricular fibrillation, although experienced electrocardiographers might suspect auricular flutter. The EA lead clearly demonstrates that the mechanism is auricular flutter with varying block. The R waves are marked at the top and the P waves at the bottom of the EA record.

Fig. 4.—No P waves are apparent in the standard leads, but the EA lead shows a notching of the descending limb of S wave which represents the P wave. For comparison, a small portion of a tracing from the same level after return to normal rhythm is included. It can be seen that the P wave is now in its normal position in front of the QRS and the notching of the descending limb of the S wave has disappeared. This establishes a diagnosis of nodal tachycardia.

interval will vary from day to day, or accelerating the pulse by administration of atropine or by exercise will shift the P wave from the T wave so that it becomes visible. In this particular case the P-R interval returned to normal over a period of several weeks.

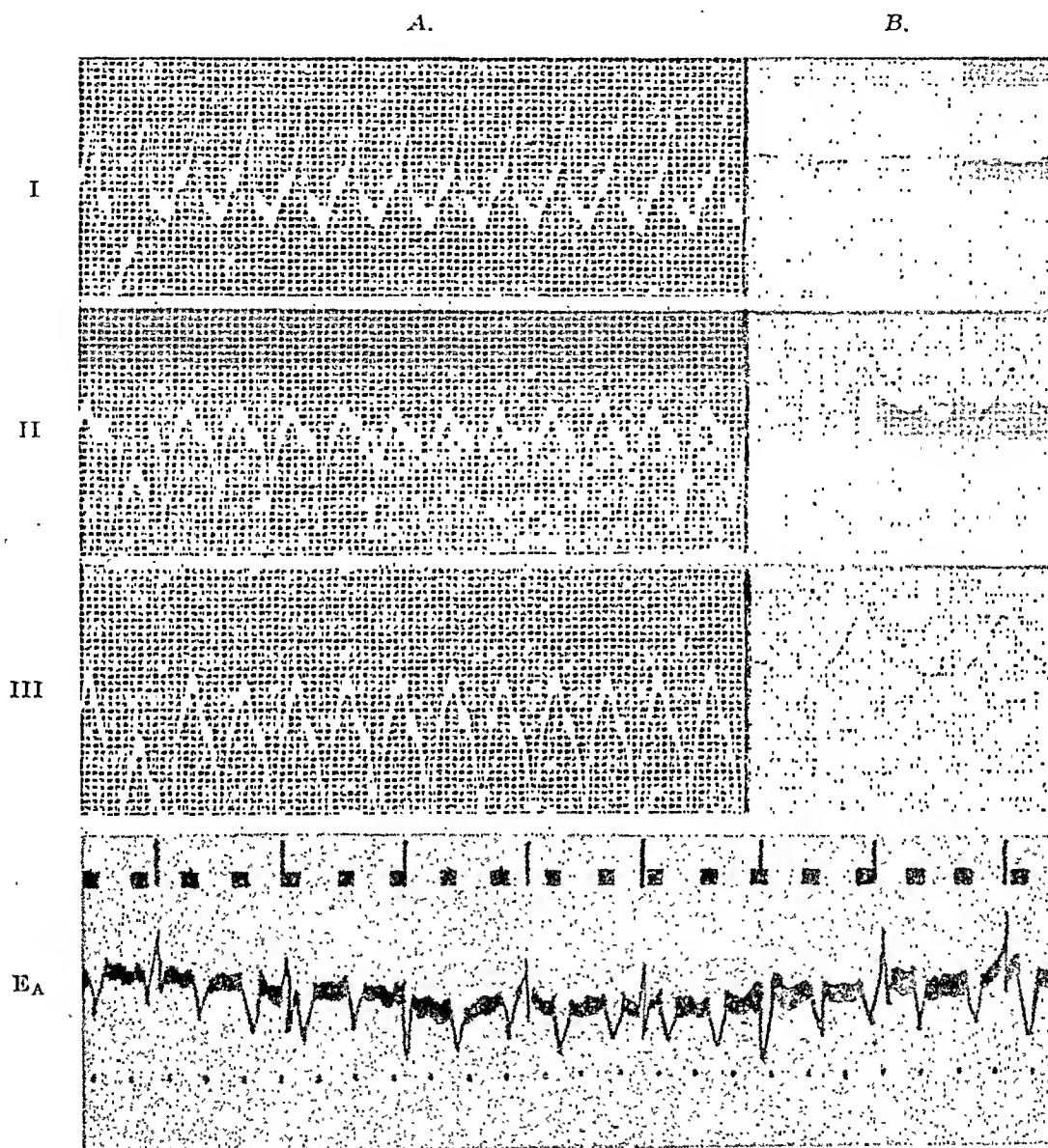


Fig. 5.—The leads under B show a marked ventricular conduction defect (RBBB) which was present prior to the tachycardia shown under A. Under these circumstances it seemed impossible to decide if this was a case of supraventricular tachycardia with a ventricular conduction defect or a ventricular tachycardia. The E_A lead definitely established the diagnosis of ventricular tachycardia. The small blocks at the top of the record represent the QRS complexes and the vertical lines, the P waves showing an independent auricular rhythm much slower than that of the ventricles. (The E_A lead is an exact tracing of the electrocardiogram and was made solely to improve reproduction.)

The electrocardiogram in Fig. 2 illustrates the type of case in which the voltage of the P wave is too low to make identification positive. There are suggestive P waves in Leads II and III, but they are not definite enough to be convincing. From the auricular level of the esophagus, however, the P waves stand out well and it is clearly seen that the auricles have an independent rhythm slower than that of the ventricles.

In Fig. 3 the rate is rapid and irregular, although there are sequences which seem fairly regular. No definite P waves can be identified, and the most obvious diagnosis would be rapid auricular fibrillation although experienced electrocardiographers would suspect flutter. The esophageal lead at the auricular level (E_A) reveals definite flutter waves which are perfectly regular at a rate of 300 per minute in contrast to the ventricular rate of about 140.



Fig. 6.—This is the electrocardiogram of a 44-year-old man during an episode of tachycardia which occurred one week after an acute anterior myocardial infarction. The esophageal electrocardiogram shows very large P waves at a slower rhythm than that of the ventricles.

Fig. 4 illustrates a case of paroxysmal tachycardia which was assumed to be nodal rhythm because no P-waves could be identified in the standard leads. The esophageal lead revealed the P wave on the descending limb of the S wave. A tracing from the same level after return to normal sinus rhythm is also included and the P waves are clearly present before each QRS complex, and the notching on the downstroke of the S wave has disappeared although the remainder of the QRS and the T waves have not been altered. This proves the original assumption of nodal rhythm.

Fig. 5 shows electrocardiograms of a 52-year-old man who was subject to frequent attacks of paroxysmal tachycardia. It is of interest that electrocardiograms taken during periods of normal rhythm (B) revealed a marked intra-

ventricular conduction disturbance. When we succeeded in obtaining a record during an episode of tachycardia (4), it had the appearance of a ventricular tachycardia, but because of the previous conduction disturbance, it was not clear whether this was a true ventricular tachycardia or a supraventricular tachycardia in the presence of the previously demonstrated ventricular conduction disturbance. An esophageal electrocardiogram was therefore recorded, an actual tracing of which is shown at the bottom of Fig. 5. (A tracing is used rather than the original record solely to improve reproduction.) The small blocks at the top of the tracing represent QRS complexes and the vertical lines represent P waves. This record clearly shows a slow auricular rate independent of the ventricular rate and establishes the diagnosis of ventricular tachycardia.

The last illustration (Fig. 6) shows the electrocardiogram taken on a 44-year-old man during an episode of sudden tachycardia which occurred one week after an acute anterior myocardial infarction. The standard leads were not considered sufficiently diagnostic to differentiate between auricular tachycardia, nodal tachycardia, auricular flutter, and ventricular tachycardia, so an esophageal electrocardiogram was taken. This procedure did not upset the patient in any way. The E_A lead shows very large P waves which overshadow the QRS complexes. These waves were at a slower rate and independent of the ventricular complexes, showing that the origin of the tachycardia was below the auricles. The patient was treated with large doses of quinidine sulfate by mouth and the abnormal rhythm was converted to a normal sinus rhythm within a few hours. Further convalescence was uneventful. Leads from the ventricular level of the esophagus (not illustrated) revealed a characteristic depression of the S-T segments which is commonly seen with anterior myocardial infarction.

DISCUSSION

Our purpose in presenting this material is to emphasize the value of the esophageal electrocardiogram in making accurate diagnosis in certain cases of tachycardia and arrhythmia. We feel this procedure has, in general, been neglected. The records are easy to take and simple to interpret after a short period of orientation.

Accurate interpretation is important not only to further our knowledge of electrocardiography and to prevent inaccurate diagnosis from infiltrating the literature, but also because of the necessity of having an accurate diagnosis on which to base proper therapy.

SUMMARY

1. Several electrocardiograms are reproduced, illustrating the value of the esophageal electrocardiogram in accurately diagnosing certain types of arrhythmia and tachycardia.
2. A plea has been made for more frequent use of the esophageal electrocardiogram in selected cases.

REFERENCES

1. Lieberman, Abraham, and Liberson, Frank: An Internal Electrocardiographic Lead, *Proc. Soc. Exper. Biol. & Med.* **31**: 441, 1934.
2. Brown W. Hurst: A Study of the Esophageal Lead in Clinical Electrocardiography, *AM. HEART J.* **12**: 1, 307, 1936.
3. Neboer, J.: The Esophageal Electrocardiogram in Coronary Thrombosis, *J. Clin. Investigation* **18**: 495, 1939.
4. Neboer, J., and Hamilton, J. G. M.: Oesophageal Electrocardiograms in Auricular Fibrillation, *Brit. Heart J.* **2**: 263, 1940.
5. Wolferth, Charles C., Bellett, Samuel, Livezey, Mary M., and Murphy, Franklin D.: Negative Displacement of the RS-T Segment in the Electrocardiogram and Its Relationship to Positive Displacement; an Experimental Study, *AM. HEART J.* **29**: 220, 1945.
6. Rosenbaum, Francis F., Hecht, Hans H., Wilson, Frank N., and Johnston, Franklin D.: The Potential Variations of the Thorax and the Esophagus in Anomalous Atrioventricular Excitation (Wolff-Parkinson-White Syndrome), *AM. HEART J.* **29**: 281, 1945.
7. Luisada, Aldo: A Review of Advances in the Study of Auricular Disorders, *J. Lab. & Clin. Med.* **25**: 1146, 1940.

ANOXEMIA AND EXERCISE TESTS IN THE DIAGNOSIS OF CORONARY DISEASE

GUNNAR BIÖRCK, M.D.
STOCKHOLM, SWEDEN

SINCE the usefulness of functional tests in the diagnosis of coronary heart disease still seems to be under discussion, this paper attempts to answer some of the questions pertaining to this matter from a clinical point of view.

According to Blumgart and co-workers,¹ coronary heart disease comprises angina pectoris, coronary failure, and acute myocardial infarction. In the last two conditions the patient is seriously ill and no consideration will be given to the aid that functional tests afford in making the diagnosis. The application of improved diagnostic measures will be limited to angina pectoris. Does the clinical management of angina pectoris require methods of study other than the history, physical examination, electrocardiogram, roentgenogram, and ordinary laboratory tests? Some experienced clinicians perhaps would answer in the negative. They feel sure that the diagnosis is best made from the history and usual clinical examination. Others feel a need for more objective methods in dealing with a condition which is subjective in its manifestations.

White² has stated that 25 per cent of his patients with a history of angina do not show any abnormality of the heart by the usual methods of examination. In about 150 of our patients with suspected angina (perhaps a somewhat less well-defined group than White's) the diagnosis of this condition was reasonably certain in only one-sixth; of the others, coronary artery disease was strongly suspected in two-thirds, and in one-sixth the diagnosis was in doubt. With the increasing incidence of cardiac neuroses, social and military benefits, and, perhaps, compulsory health insurance, the needs for improved objective diagnostic measures are definite. For experimental purposes and for studies before and after surgical procedures on the heart they are also useful beyond question.

For which types of patients are tests especially desirable? There are three groups to be dealt with: (1) patients with some sort of disorder in the chest, very slightly suggestive of angina; (2) patients whose symptoms resemble those of angina, but whose chest pain is mild or otherwise atypical; and (3) patients with clear-cut angina, with or without previous myocardial infarction.

The main purpose of "coronary" tests is to reveal a latent coronary insufficiency. This means that tests are indicated in suspected cases without a "coronary" electrocardiogram at rest. It is also likely that additional strain brought about by tests, even in patients with a coronary electrocardiogram at rest, will give some evidence of the remaining so-called "coronary reserve."

Even if one admits that in the first group of patients with slightly suspected angina the use of "coronary" tests can be confined to those in whom no other

From the Sabbatsberg's Hospital.

Read before the Harvard Medical Society, Boston, Feb. 12, 1946.

Received for publication May 9, 1945.

positive diagnosis could be obtained and, also, that in the third group, the members of which give a very convincing history of angina and usually some positive findings on clinical examination, the use of the tests is of limited value, there still remains the large second group of patients with moderately suspected angina, many of whom will not show evidence of coronary insufficiency in the electrocardiogram at rest. This is the group in which tests, from a diagnostic standpoint, are most desirable. With regard to the determination of the "coronary reserve" in patients with a coronary electrocardiogram at rest, it is too early to evaluate its prognostic significance. Sufficient statistics are as yet not available. As long as that problem is not solved, it is reasonable to continue to perform the tests also in this group of patients for later follow-up studies.

Assuming that tests are desirable, how should they be planned? Anginal pain and its equivalents are supposed to represent, clinically, a local ischemia of the myocardium, as do the electrocardiographic findings usually mentioned as evidence of coronary insufficiency. The test should, therefore, provoke pathologic changes in the coronary circulation and cause a relative disproportion between the demands of the myocardium for oxygenation and the supply of oxyhemoglobin through the coronary blood flow, thus eliciting either anginal pain or typical electrocardiographic changes, or both.

There are at least three ways to provoke such conditions and responses. One can reduce the oxygen saturation of the blood, either by giving a patient a gas mixture which is deficient in oxygen or by using a low-pressure chamber; one can exercise the patient, which increases the cardiac demand for oxygen without reducing the supply; or one can increase the work of the heart by adrenalin, which is a very dangerous method that we have not used. Apart from other considerations, the first method, the anoxemia test, is probably to be preferred for the study of the coronary circulation per se, and the second one, the exercise test, for the estimation of its capacity in the more natural environment of the whole system of reflexes, body metabolism, and hormonal activity.

In the anoxemia test (in Sweden we prefer to call it the hypoxemia test) we use, according to the technique devised by Levy and associates,³ 10 per cent oxygen and 90 per cent nitrogen breathed for twenty minutes, or less in case definite anginal pain or other unpleasant reactions should develop. Immediately after finishing the test, the patient is allowed to breathe 100 per cent oxygen for at least five minutes. We have also felt it wise, for the sake of comparison, to use the original criteria of Levy and co-workers^{3b} in the interpretation of the electrocardiographic findings (Table I). In a later paper^d they discarded their fourth criterion.

There are at least two remarks to be made about the discrepancy between the theory and the reality of this test. The first concerns the oxygen saturation of the blood. Because of different types of breathing during the period of anoxemia, even in case of good pulmonary function, the oxygen saturation of the arterial blood, and probably also the carbon dioxide content and the pH of the blood, will differ from patient to patient. The same oxygen percentage in the inspired air will mean, to some extent, different things to different patients.

TABLE I. CRITERIA

Anoxemia.—The test is positive if any one of the following is found:

1. The arithmetic sum of the S-T deviations in Leads I, II, III, and IV F is greater by 3 mm. or more than in the control.
2. There is partial or complete reversal of the direction of the T wave in Lead I, accompanied by an S-T deviation of 1 mm. or more in this lead.
3. There is complete reversal of the direction of the T wave in Lead IV F, regardless of any S-T deviation in this lead.
4. There is partial reversal of the direction of the T wave in Lead IV F, accompanied by an S-T deviation of 1 mm. or more in this lead.

Exercise (New, "rigid" set of criteria)*.—The test is positive if:

1. The S-T depressions in Leads I, II, and III exceed together 2 mm.
2. T_1 or T_2 are inverted.
3. T_1 is diphasic and $S-T_1$ is depressed at least 1 mm.
4. Any single S-T depression is 1.5 mm. or more.

*These are to be regarded only as an attempt to establish better criteria than we formerly had. They may be changed following further experience and later follow-up studies.

Perhaps this objection can be met by using the Millikan oximeter for serial readings. If it works well, it is possible that the test, in the future, can be standardized according to the oxygen saturation of the blood rather than by the oxygen percentage in the inspired air.

The other objection to be discussed concerns the interpretation of the so-called coronary changes that appear in the electrocardiogram. There is still (perhaps now more than at any time) much obscurity about the underlying mechanism both with regard to the production of pain and with regard to the electrocardiographic signs of coronary insufficiency. The number of causal explanations is still increasing, and the importance of functional influences is more and more stressed. Such criticism is correct. It is obvious that further electrocardiographic, biochemical, and physiologic studies are greatly needed. But, in my opinion, this criticism should not retard attempts to gain further information about the reactions of the heart with diseased coronary arteries. It may, however, dispose us to a certain caution in our interpretation of the tests.

With this in mind, how does the anoxemia test work out clinically? In Table II are shown the results with anoxemia tests which have been published by Larsen (1938),⁴ by Levy and associates (1941)^{3b, 3c} and by Pruitt, Burchell, and Barnes (1945),⁵ together with our own material which has been collected since 1942, when the test was introduced in Sweden by Dr. Gustav Nylin. In 1944, I had the opportunity to make the first survey of the test's results.⁶ The report of Burnett, Nims, and Josephson⁷ is not included since the use of a different oxygen tension of gas mixture prevents a comparison of their results with ours.

Table II is made up with regard to the previously mentioned three groups of patients with suspected angina, and the published statistics are classified according to these groups. Contrary to the procedure of the others, my clinical classification has been made without knowing the form of the electrocardiogram at rest.

TABLE II. COMPARISON BETWEEN PERCENTAGE OF POSITIVE ANOXEMIA TESTS IN THREE MAIN CLINICAL GROUPS, COMPILED FROM REPORTS OF VARIOUS INVESTIGATORS

INVESTIGATOR	GROUP I NORMALS AND SLIGHTLY SUSPECTED "CORONARY" CASES		GROUP II MODERATELY SUSPECTED "CORONARY" CASES		GROUP III PROBABLE OR CERTAIN "CORONARY" CASES	
	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
Larsen (1938) ^a (9% O ₂)	28	0	26	15	17	77
Levy (1941) ^{ab}	115	0	33	18	22 73	31* 55†
Pruitt, Burchell, and Barnes (1945) ^c	89	1.1	108	19.5	92	53
Borck (1946) ^e	149	2.7‡	131	19.8	46 20	30 40§

*No anginal pain.

†Anginal pain.

‡Four positive tests in cases with definite pulmonary disease or other types of heart disease but no "coronary" symptoms.

§Abnormal ECG at rest.

There seem to be four conclusions to be drawn from Table II: (1) There are no positive tests in the group of normal subjects or patients with slightly suspected angina, if evidence of other cardiac disease, definite respiratory impairment, or severe anemia is ruled out. (2) One will have to expect about 20 per cent positive tests in the moderately suspected group. This figure is surprisingly constant throughout the three series of statistics which are based upon identical technique and criteria. In my material the figure is 18 per cent in 100 patients without a coronary electrocardiogram at rest, and 27 per cent in thirty-one with a coronary electrocardiogram at rest; in the whole group, it is 19.8 per cent. (3) Between 30 and 50 per cent of the patients with probable or certain coronary disease will show a positive test. (4) The conclusion follows that a negative test does not exclude the existence of coronary disease. Since Table II is based upon a study of 939 cases it should have statistical significance.

What is the correlation between the outcome of the test and the findings at autopsy? Although functional influences may be of some importance in the production of the anginal syndrome, we must, for the verification of our diagnosis, rely on the anatomic findings. Table III shows a comparison between the results of the anoxemia tests and the post-mortem findings, or, when no post-mortem study was performed, the type of death: an acute death, which probably resulted from myocardial infarction, ventricular fibrillation, or asystole; or, in contrast, death from progressive congestive failure or from intercurrent disease. The figures are collected from Levy's publications and from our material. The series thus studied is not as yet very large, but the results are rather striking.

TABLE III. CORRELATION BETWEEN RESULTS OF ANOXEMIA TESTS AND CONDITION OF CORONARY VESSELS AT AUTOPSY OR TYPE OF DEATH

	POST-MORTEM FINDINGS				NO POST-MORTEM TYPE OF DEATH			
	MARKED CORONARY SCLEROSIS		SLIGHT OR NO CORONARY SCLEROSIS		ACUTE DEATH		CONGESTIVE FAILURE	
	LEVY ^{3c}	BIÖRCK ⁶	LEVY ^{3c}	BIÖRCK ⁶	LEVY ^{3c}	BIÖRCK ⁶	LEVY ^{3c}	BIÖRCK ⁶
Positive tests	1	1	—	—	5	1	—	—
Negative tests								
Abnormal ECG at rest	2	2	—	—	1	2	3	—
Normal ECG at rest	—	—	1	2		—		2
Negative tests with anginal pain					4	1?		

It will be of great interest to follow up a larger autopsy series. For our part, we have also separated a group of "doubtful" cases, with electrocardiograms definitely changed, but not sufficiently so to fit in with Levy's rather rigid criteria; we intend to follow this group also in order to estimate the significance of such slighter changes.

It is the general experience that in some cases the test can change from positive to negative after an interval of time has elapsed. This may be ascribed, in part, to so-called functional influences, but it may also be the expression of substantial changes in the coronary circulation. The development of coronary sclerosis is not a constantly progressive process but one which occurs stepwise. A sudden narrowing or occlusion may produce a state of impending infarction, accidentally disclosed by a test; at the time of the next test a sufficient collateral circulation may have been established to result in a negative test. It is possible that a stable positive test is a more favorable sign than a changing one, for the latter may indicate either an active sclerotic process or a functional instability, both equally undesirable.

In this connection it is proper to discuss the hazard of the test. Table IV shows the unpleasant reactions which have been reported. . In addition to these figures, there may be mentioned two other cases of pulmonary edema in Levy's earliest cases, and two vasovagal reactions which occurred in our clinic in 1945. The vasovagal reactions are probably partly unavoidable; they are usually not accompanied by coronary tracings, and they are, with proper observation and treatment, harmless. Psychogenic reactions are likewise hard to avoid because some of these cases cannot be valued without the test. If the test is performed on proper indications, if the technique is well controlled, and if the observation of the patient is careful, trouble should not occur.

TABLE IV. UNPLEASANT REACTIONS DURING ANOXEMIA TEST

	LEVY ^{3b}	LEVY ^{3c}	PRUITT, BURCHELL, AND BARNES ⁵	BIÖRCK ⁶
Total number of patients	262	137	289	326
Reactions				
Vasovagal syncope	12 (11)*	8 (6)	9	1
Unconsciousness		2 (1)	3	
Convulsions	1			
Cardiac arrhythmia			3	?
Pulmonary edema		1		
Severe anxiety; hysteria	1	5 (3)	1	1

*Figures in brackets indicate number of patients with that reaction.

In some cases the test brings about severe anginal pain without marked changes in the electrocardiogram at the time it is interrupted. If there is real anginal pain, which is, in some cases, hard to judge objectively, Levy's and also our experience is that coronary disease is very probable. It is possible that an ischemic area, not located near either the endocardium or the epicardium, can be responsible for this circumstance. It is also possible that cardiac pain can arise in the walls of the coronary vessels. As the anoxemia test, as well as other tests, should be regarded only as an aid to the clinical diagnosis, we probably still should limit the criteria of a positive test to objective findings, although we may feel quite free to evaluate the provocation of pain for what it may be worth in our clinical conception of the patients' state.

Finally, a few words about exercise tests. In the United States these tests have been studied and used by Master⁸ and Riseman and co-workers.⁹ These investigators have used a two-step test; Master has used standardized work while Riseman and co-workers have continued exercise until pain appeared. In performing the exercise test, we have used Nylin's staircase, which is also used for functional studies of the oxygen consumption. The work is generally standardized to 5 rounds at a rate of 160 steps per minute, which most patients whom we expose to this test are able to perform without pathologic increase of their oxygen debt. Our opinion is that exercise tests should be standardized if the results are to be judged by the electrocardiograms. If the patients are allowed to work until they experience pain (which is a subjective limit), it is more logical to judge results from the amount of work performed rather than from changes in the electrocardiograms. The time between the completion of the work and the taking of the electrocardiograms is of importance. We have had the privilege of working with Elmqvist's electrocardiographic instrument, which simultaneously records five leads on the same piece of photographic paper.

Because of the differences in technique, it is hard to compare our results with those obtained by American workers. There is also the question of criteria. None of those who have written on exercise tests has used the same criteria. It is our experience that, in the case of exercise tests, much of their usefulness depends

upon the criteria applied. Formerly, we used very liberal criteria for positive tests. Since we found that about 25 per cent of the positive tests were obtained in those in whom coronary artery disease was not suspected (Group I of Table V), we now apply more rigid criteria which are very similar to those employed in the anoxemia test. Table V shows a comparison, in a series of 178 patients, of the results of the anoxemia test with those of the exercise test, the latter judged by means of both our old and our new criteria. Of 178 patients tested, 154 gave a negative result with both tests. In twenty-nine, the anoxemia tests showed a greater number of positive results than did the exercise test; in fourteen, the exercise test gave the greater number of positive results. The conclusion, therefore, seems justified that these tests should be used side by side in order to give a more comprehensive view of the condition. Having used both tests, we are of the opinion that they are about equally safe in the average patient, that the exercise test is perhaps a little simpler to perform, and that the anoxemia test probably gives more useful information than does the exercise test. Master and associates¹⁰ have recently compared the effects of their two-step test with the effects of the anoxemia test, done by the Levy method, in 117 persons. They found that both tests gave similar results. They have, however, regarded the exercise test as positive if any S-T segment was deviated more than 0.5 mm. or if the T wave became inverted in any lead. These criteria are, in our experience, far too liberal. The question is, after all, not to obtain the largest possible number of positive tests but to obtain positive tests which, with certainty, correspond to the physiopathologic condition for which the test is intended.

TABLE V. COMPARISON BETWEEN ANOXEMIA AND EXERCISE TESTS

GROUP	ANOXEMIA		EXERCISE			
	POSITIVE	DOUBTFUL	OLD CRITERIA		NEW CRITERIA	
			POSITIVE	DOUBTFUL	POSITIVE	DOUBTFUL
I. Without suspected coronary disease	1	4	6	5	2	4
II. With suspected coronary disease	11	7	12	2	7	3
III. With probable or certain coronary disease	7	7	6	3	5	1
	19	18	24	10	14	8
	37		34		22	

As a general conclusion concerning the usefulness of these tests, the following may be said. Because they require technical equipment, a careful general examination of the patient with regard to indications and contraindications, and a certain experience with regard to their interpretation, and also because they

involve a slight chance of unpleasant and perhaps alarming reactions, they are not to be recommended for general use. Where possible, it is preferable to refer candidates for the test to a special heart service. In heart clinics and laboratories where experimental studies concerning "coronary" problems are carried out, these tests should be used. The first series of cases may be disappointing; that was our first impression. But only sufficient statistics can give the proper answer.

REFERENCES

1. Blumgart, H. L., Schesinger, M. J., and Zoll, P. M.: Angina Pectoris, Coronary Failure and Acute Myocardial Infarction: The Role of Coronary Occlusions and Collateral Circulation, *J.A.M.A.* 116: 91, 1941.
2. White, P. D.: Heart Disease, ed. 3, New York, 1944, The Macmillan Co.
3. a. Levy, R. L., Bruenn, H. G., and Russell, N. G., Jr.: The Use of Electrocardiographic Changes Caused by Induced Anoxemia as a Test for Coronary Insufficiency, *Am. J. M. Sc.* 197: 241, 1939.
b. Levy, R. L., Williams, N. E., Bruenn, H. G., and Carr, H. A.: The "Anoxemia Test" in the Diagnosis of Coronary Insufficiency, *AM. HEART J.* 21: 634, 1941.
c. Levy, R. L., Patterson, J. E., Clark, T. W., and Bruenn, H. G.: The "Anoxemia Test" as an Index of the Coronary Reserve, *J.A.M.A.* 117: 2113, 1941.
d. Patterson, J. E., Clark, T. W., and Levy, R. L.: A Comparison of Electrocardiographic Changes Observed During the "Anoxemia Test" on Normal Persons and on Patients With Coronary Sclerosis, *AM. HEART J.* 23: 837, 1942.
4. Larsen, K. H.: Om Forandringer i Elektrokardiogrammet Hos Sunde Og Syge Under Experimental Iltmangel, Copenhagen, 1938, Ejnar Munksgaards Forlag.
5. Pruitt, R. D., Burchell, H. B., and Barnes, A. R.: The Anoxia Test in the Diagnosis of Coronary Insufficiency: A Study of 289 Cases, *J.A.M.A.* 128: 839, 1945.
6. Björck, Gunnar: Hypoxaemia Tests in Coronary Disease, *Brit. Heart J.* 8: 17, 1946.
7. Burnett, C. T., Nims, M. G., and Josephson, C. J.: The Induced Anoxemia Test: A Study by Age Groups, *AM. HEART J.* 23: 306, 1942.
8. Master, A. M.: The Two-Step Test of Myocardial Function, *AM. HEART J.* 10: 495, 1935.
9. Riseman, J. E. F., Waller, J. V., and Brown, M. G.: The Electrocardiogram During Attacks of Angina Pectoris: Its Characteristics and Diagnostic Significance, *AM. HEART J.* 19: 683, 1940.
10. Master, A. M., Nuzie, S., Brown, R. C., and Parker, R. C., Jr.: The Electrocardiogram and the "Two-Step" Exercise: A Test of Cardiac Function and Coronary Insufficiency, *Am. J. M. Sc.* 207: 435, 1944.

PLASMA CONCENTRATIONS OF QUINIDINE WITH PARTICULAR REFERENCE TO THERAPEUTICALLY EFFECTIVE LEVELS IN TWO CASES OF PAROXYSMAL NODAL TACHYCARDIA

ALLEN F. DELEVETT, M.D.,* AND CHARLES A. POINDEXTER, M.D.†
NEW YORK, N. Y.

IN THE past, methods for the estimation of cinchona alkaloids in biologic fluids and tissue were technically difficult and relatively insensitive.¹⁻³ Recently, however, Brodie and co-workers have reported new methods, based on colorimetry, which obviate these objections.^{4,6}

The purpose of this paper is to report (1) plasma concentrations of quinidine in nineteen patients after a single oral dose of 1.0 Gm. of quinidine sulfate and (2) the therapeutic range of plasma concentration of quinidine in two cases of paroxysmal nodal tachycardia.

METHODS

The colorimetric method developed by Brodie⁶ was used for the estimation of plasma quinidine concentrations in this study. This method involves the extraction of the alkaloid from alkalinized plasma by means of ethylene dichloride. Acid degeneration products, presumably phenolic in character, are then removed from the organic phase by means of an alkalinized alcoholic wash. Next the ethylene dichloride and contained alkaloid are shaken with methyl orange. The result of this step is the formation of a colored compound of the alkaloid and the dye. Measurement of the optical density of this compound is then made in the Evelyn photoelectric colorimeter against suitably prepared standards. With each set of plasma determinations, one or more recoveries were run, of which the majority fell within 90 to 100 per cent.

Nineteen adult patients (nine men and ten women, whose ages ranged from 20 to 60 years) were given a single dose of 1.0 Gm. of quinidine sulfate orally. These patients were selected so as to exclude obvious gastrointestinal, liver, and renal disease, thus minimizing possible interference with the normal processes of absorption, localization, degradation, and excretion of the alkaloid. All of the patients were confined to bed during the test. Sixteen of them ate regular meals. Of these, the majority received the 1.0 Gm. dose one to one and one-half hours before breakfast, while the others received the quinidine several hours after breakfast or after the noon meal. The remaining three patients of the nineteen were fasting for the eight hours preceding and the eight hours following the drug.

Blood specimens were collected in most instances every fifteen minutes for the first hour after the oral dose of the drug, and then at two, three, four, six,

Received for publication April 29, 1946.

*Oliver Rea Fellow in Cardiology, New York Post-Graduate Medical School and Hospital, Columbia University.

†From the Department of Medicine, Division of Cardiology, New York Post-Graduate Medical School and Hospital, Columbia University.

and eight hours. Ten patients also had levels taken at ten and twelve hours, and six at twenty-four hours.

The dose of 1.0 Gm. of quinidine sulfate was decided upon because of the possibility of inaccuracy with the colorimetric method at plasma quinidine concentrations much lower than those afforded by this quantity. In order to insure accurate dosage, the contents of each capsule of the drug had been carefully weighed.

Two ambulatory patients with paroxysmal nodal tachycardia were also studied over a period of four and one-half months, during which time observations were made on the relationship between varying plasma concentrations and therapeutic effect. A therapeutic regime was established for both patients in which a fixed dose of quinidine sulfate was given at four-hour intervals, day and night, for periods of from three to four weeks, during which periods stabilized plasma levels were obtained. The dose of the drug was progressively reduced by 25 per cent with each successive period. Blood samples were drawn from four to twelve times a week, usually three hours after the nearest dose. An inquiry into any symptoms and a recording of the pulse were made at each bleeding. Occasionally the effect of exercise upon the pulse rate was also recorded. Electrocardiograms were taken whenever an attack of tachycardia occurred and following reconversion to regular sinus rhythm.

RESULTS

1. *Plasma Concentrations Attained in Nineteen Patients After a Single Oral Dose of Quinidine Sulfate.*—Table I and Figs. 1 and 2 show the relationship of plasma concentration to time after a single oral dose of 1.0 Gm. of quinidine sulfate. The patients on whom data are given in Fig. 1 had the eight-hour

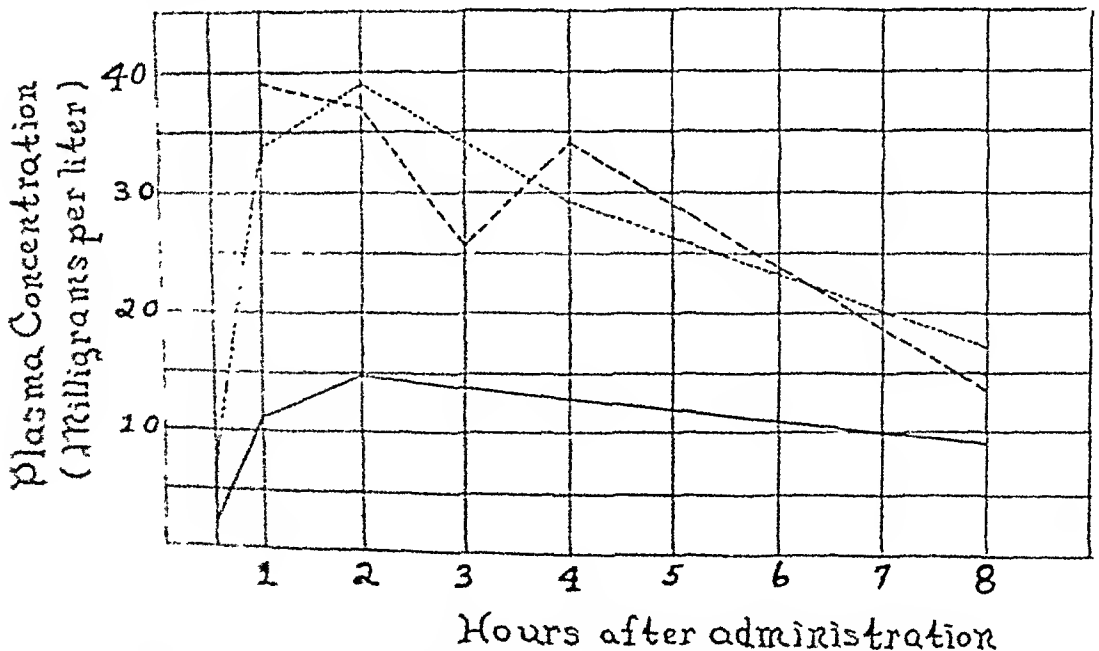


FIG. 1. Quinidine plasma concentration curves in three patients given 1.0 Gm. of quinidine sulfate as a single oral dose. (Fasting subjects.)

TABLE I. SUMMARY OF PERTINENT DATA ON EACH OF TWENTY PATIENTS GIVEN 1.0 GM OF QUINIDINE SULFATE ORALLY

PATIENT	1	2	3	4	5	6	7	8	9	10
SEX	M	M	M	F	M	F	F	F	F	F
HEIGHT	5' 9½"	5' 4"	5' 4"		5' 4"	5' 3"	5' 5"	5' 5"	5' 1"	5' 1"
WEIGHT	151	143	137		185	135	112	132	106	101
<i>Quinidine blood levels</i> (mg./liter plasma)										
15 min.	0.00	0.48	0.12	0.12	0.00	0.28	0.20	0.00	1.28	0.00
30 min.	0.20	2.88	1.44	0.00	0.00	1.68	0.60	0.00	2.68	1.68
45 min.	0.48	2.08	1.96	0.40	0.24	1.50	0.88	0.12	3.66	2.88
1 hr.	0.52	2.28	2.04	0.70	0.68	1.84	1.52	0.28	3.72	2.88
2 hr.	2.04	3.36	2.12	2.76	0.92	2.00	3.52	1.28	2.88	3.64
3 hr.	2.08	3.12	2.04	2.84	1.52	1.80	3.48	2.28	2.24	3.84
4 hr.	2.04	2.48	1.80	3.40	1.72	1.80	2.76	2.40	1.92	2.92
6 hr.	2.00	1.92	1.68	3.00	1.08	1.52	2.04	2.04	1.40	2.08
8 hr.	1.90	1.32	1.08	2.12	0.72	1.12	1.68	1.32	0.92	1.16
10 hr.			0.72				1.04	0.92	0.48	0.84
12 hr.			0.42				0.88	0.72	0.36	0.44
24 hr.			0.16						0.28	0.00
Maximum level	2.08	3.36	2.12	3.40	1.72	2.00	3.52	2.40	3.72	3.84
Time of maximum level	3 hr.	2 hr.	2 hr.	4 hr.	4 hr.	2 hr.	2 hr.	4 hr.	1 hr.	3 hr.
<i>Percentage loss in plasma concentration from time of dose</i>										
6 hr.	4%	43%	21%	12%	37%	24%	42%	15%	62%	46%
8 hr.	9%	60%	50%	37%	60%	44%	52%	45%	75%	70%
12 hr.			80%				75%	70%	87%	90%
24 hr.			92%						92%	100%
Patient	1	2	3	4	5	6	7	8	9	10
PATIENT	11	12	13	14	15	16	17	18	19	20
SEX	F	M	M	F	M	M	F	M	F	F
HEIGHT	5' 5"	5' 9"	5' 3"	5' 3"	5' 11"		5' 2"½	5' 8"	5' 0"	5' 1"
WEIGHT	119	172	146	99	140		111	129	114	92
<i>Quinidine blood levels</i> (mg./liter plasma)										
15 min.	0.36			0.20	0.00	0.48				
30 min.	0.96	0.00	0.40	0.96	0.76	1.40	0.44	0.20	0.72	
45 min.	1.56	1.20	0.88	1.32	2.56	1.80	1.24			
1 hr.	1.40	1.56	1.40	1.52	2.56	2.92	1.72		3.36	3.88
2 hr.	2.04	2.56	2.72	2.84	2.08		4.32	1.12	3.88	3.72
3 hr.	2.56	2.88	2.44	2.48	2.40		4.32	1.48		2.56
4 hr.	2.44	2.48	2.20	2.12	1.68		3.72	1.36	2.96	3.44
6 hr.	1.68	2.08	1.68	1.72	1.32		2.84			
8 hr.	1.20	1.40	1.32	1.28	0.72		2.79	0.88	1.72	1.36
10 hr.	0.64	1.12	1.20	0.76	0.60					
12 hr.	0.32	1.16	0.92	0.44	0.12		1.76			
24 hr.	0.00			0.24	0.00					
Maximum level	2.56	2.88	2.72	2.84	2.56		4.32	1.48	3.88	3.88
Time of maximum level	3 hr.	3 hr.	2 hr.	2 hr.	¾ hr.		3 hr.	2 hr.	2 hr.	1 hr.
<i>Percentage loss in plasma concentration from time of dose</i>										
6 hr.	34%	28%	40%	40%	48%		34%			
8 hr.	53%	51%	51%	55%	71%		47%	40%	56%	65%
12 hr.	88%	60%	66%	84%	95%		75%			
24 hr.	100%			92%	100%		96%			
Patient	11	12	13	14	15	16	17	18	19	20

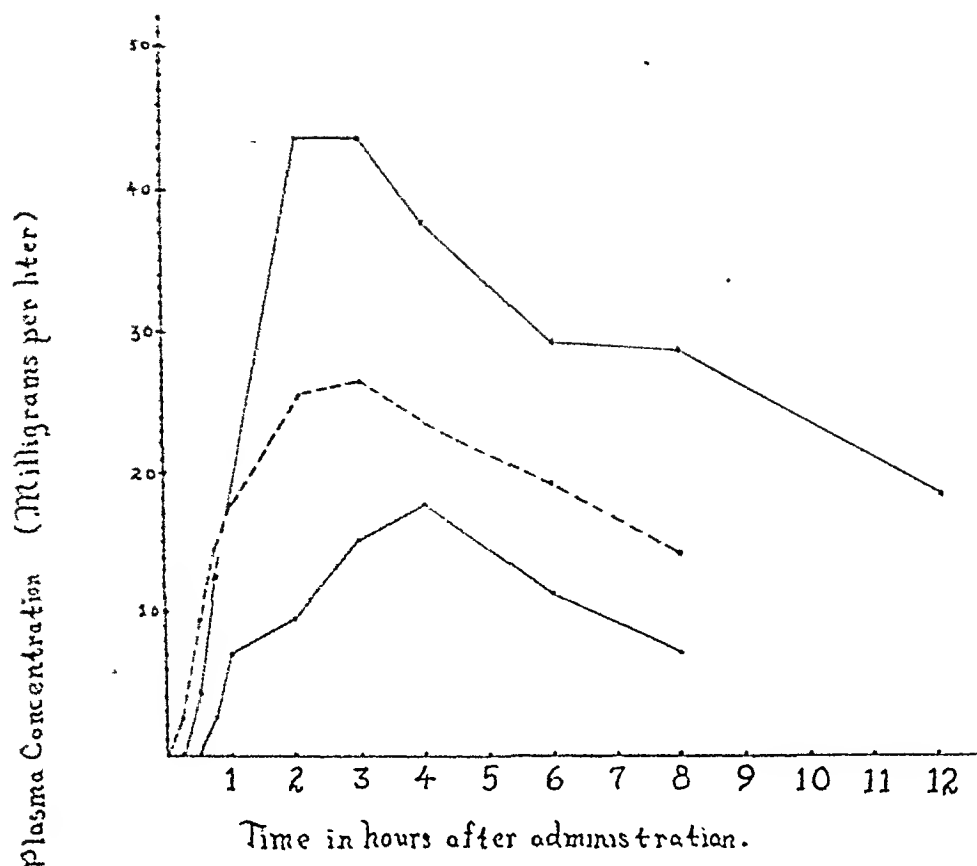


Fig. 2.—The middle curve represents the average concentration at each time period of the sixteen nonfasting patients. The upper curve is that of the patient who attained the highest plasma concentration among the sixteen patients. The lower curve is that of the patient who attained the minimum plasma concentration among the sixteen patients.

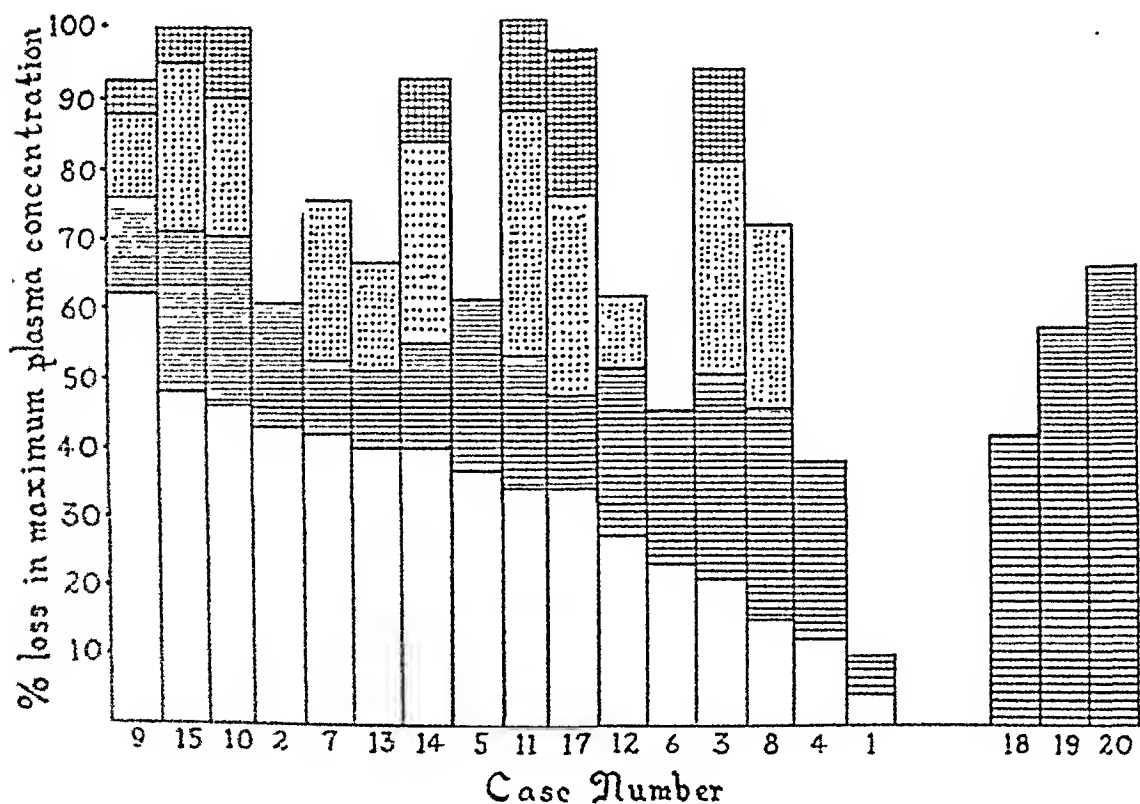


FIG. 3. Showing the per cent loss in maximum plasma concentration at six, eight, twelve, and twenty-four hours in sixteen patients given a single oral dose of 1.0 Gm. of quinidine sulfate. Blank, per cent loss at six hours; horizontal, per cent loss at eight hours; stippled, per cent loss at twelve hours; crosshatch, per cent loss at twenty-four hours.

fast before and after the dose; those on whom data are given in Fig. 2 ate the usual hospital diet. In both groups there was a considerable variation in the maximum levels attained, in the times of maximum concentration, and in the rates of fall. Maximum concentration was reached between two and four hours in 84 per cent of the cases studied. (Hiatt,⁵ also using the Brodie colorimetric method, found the maximum concentration was reached from three to four hours after the oral administration of the drug.) No regular correlation between body weight and the maximum plasma concentration was observed. As for the marked

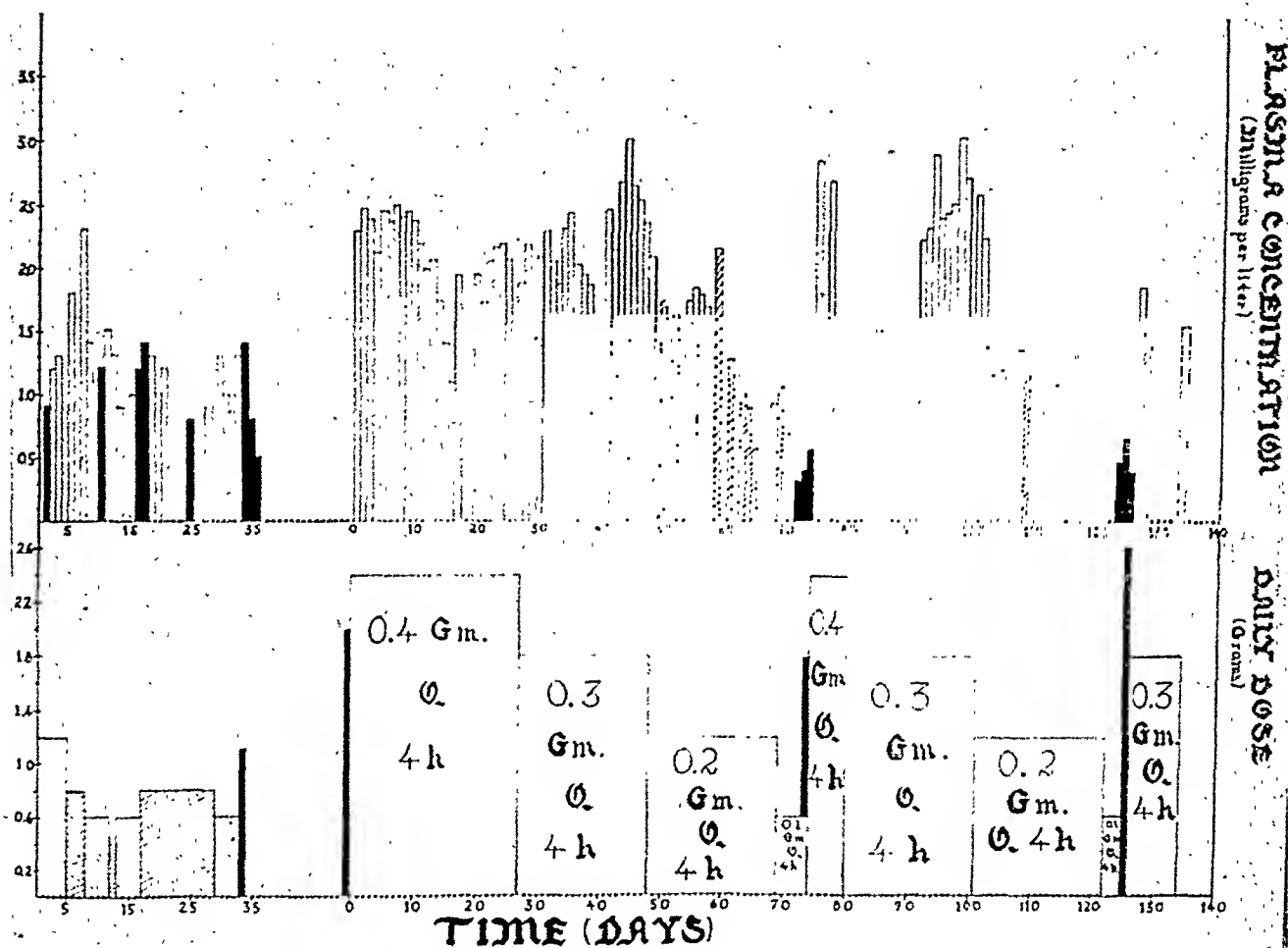


Fig. 4.—A 56-year-old white man, showing the relationship between dosage of quinidine sulfate, quinidine plasma concentrations, and the occurrence of nodal extrasystoles and paroxysmal nodal tachycardia. The diagonally lined blocks in the area of plasma concentration represent the occurrence of extrasystoles, while the solid blocks indicate the occurrence of paroxysmal nodal tachycardia. In the area of daily dose, the solid blocks represent single large doses of quinidine sulfate given to raise the plasma concentration rapidly.

Blank, dose every four hours; diagonal lines, dose every six hours; stippled, dose every eight hours; horizontal lines, dose every twelve hours.

variation in rates of fall (Fig. 3), by six hours the majority of levels had fallen between 20 and 40 per cent, with extremes from as low as 4 per cent up to as high as 62 per cent. By eight hours the fall was between 40 and 60 per cent, with extremes from 9 per cent to 75 per cent. Of the eleven patients whose levels were taken at twelve hours, all had fallen 60 per cent or more. At twenty-four hours, seven of these patients had levels which showed a fall of over 90 per cent in each. There was no apparent correlation between maximum plasma concentration and the rate of fall. Complete data for all patients is given in Table I.

2. *The Therapeutic Range of Plasma Concentration in Two Patients With Paroxysmal Nodal Tachycardia.*—Two patients with paroxysmal nodal tachycardia were studied to determine the correlation, if any, between the attack-rate frequency and various plasma quinidine concentrations. Both patients had

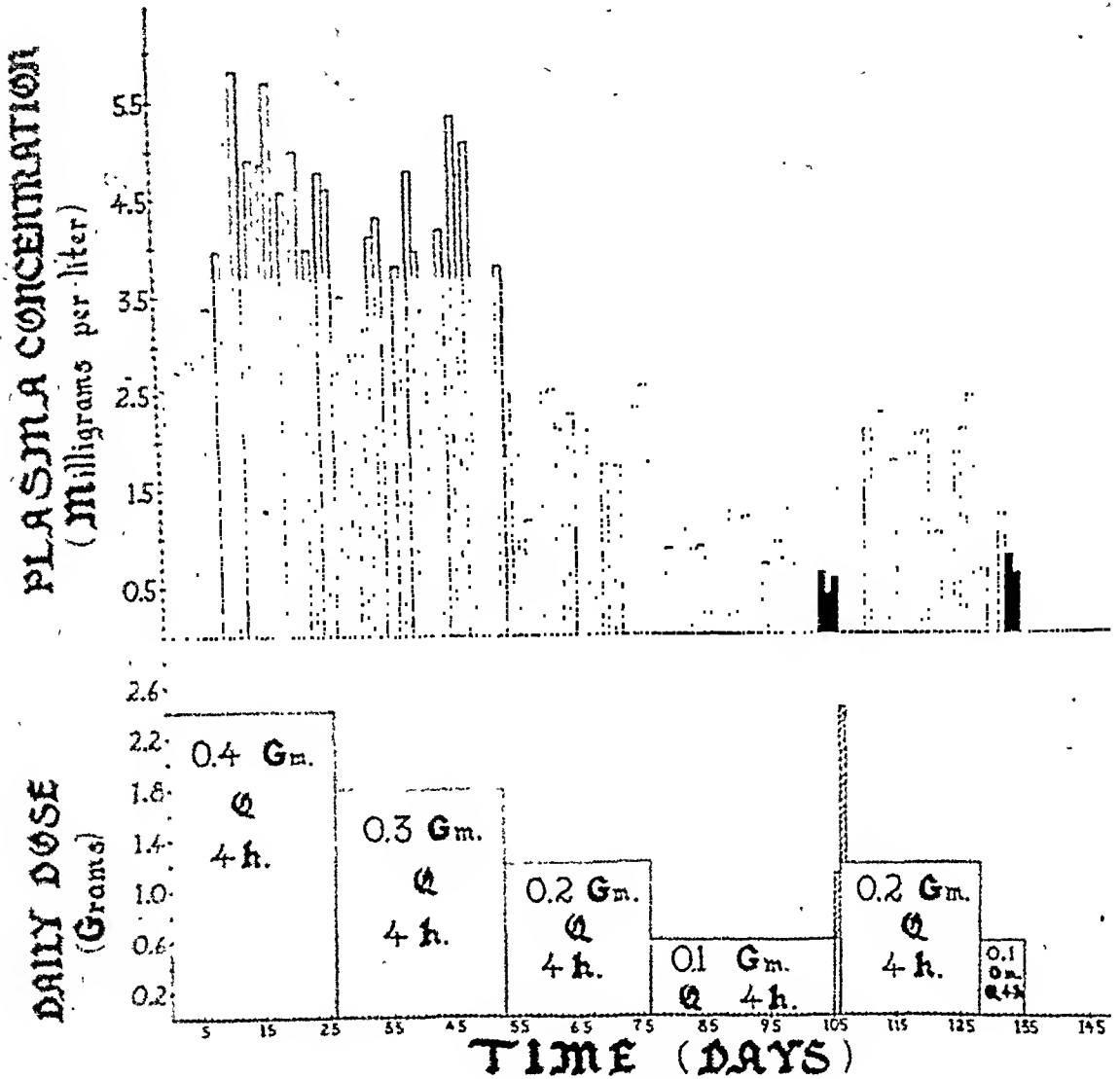


Fig. 5 — A 11-year-old white woman, showing relationship between daily dose of quinidine sulphate, plasma quinidine concentration, and the occurrence of paroxysmal nodal tachycardia. The solid blocks indicate these attacks. The diagonally lined blocks represent single large doses of quinidine sulfate given to raise the blood level rapidly.

been followed for some time before the present study was begun. One of these, G. B.,² was a man 56 years of age who had had documented paroxysmal nodal tachycardia for twelve years, with almost constant attacks for the previous three years whenever he was ambulatory. During the year preceding this study he had been unable to work. Tachycardia was even so frequent and marked that he was obliged to stop several times during his daily shave to sit down and rest. There was no evidence of organic heart disease. The other

²Plasma concentrations during the preliminary studies on this patient were determined by the quantitative method described by Brodie.

patient, S. F., a woman 41 years years of age, had had attacks at least once every three weeks, and frequently they had come as often as several times a day over as long a period as a week or ten days. She also had no evidence of organic heart disease.

After a suitable control period was established, during which time the frequency of attacks was documented, quinidine sulfate was started and given to the patients every four hours at a set dosage so that a uniform daily total intake of the drug could be maintained for varying periods* (Figs. 4 and 5). Plasma quinidine concentrations above 1.0 mg. per liter were coincident with absence of attacks. Dosages which produced plasma levels below 1.0 mg. per liter resulted in a recurrence of frequent attacks. Correlation of attack onset and plasma level was easily reproducible in these patients. (As shown by Figs. 4 and 5, in the male subject the arrhythmia appeared when the plasma levels ranged between 0.32 and 0.76 mg. per liter, while attacks were present with plasma concentrations of between 0.28 and 0.84 mg. per liter in the female patient.) Although this data does not establish an absolute critical level for all such patients, it suggests that such a level exists. Determination of critical plasma quinidine levels by means of the methods outlined in this paper is suggested as a basis for rational approach to the control of paroxysmal tachycardia.

SUMMARY AND CONCLUSIONS

1. By the use of Brodie's colorimetric method for plasma quinidine concentration determinations, levels were run on a series of patients who had taken a single large oral dose of quinidine sulfate.

2. There is a marked individual variation in maximum plasma quinidine concentration following a large single oral dose.

3. The time of maximum plasma concentration varies widely in different patients, from forty-five minutes to four hours after administration.

4. The rate of fall of plasma quinidine concentration varies markedly from patient to patient and apparently bears no relationship to the initial maximum level.

5. The correlation between plasma quinidine concentration and therapeutic effectiveness in two patients with paroxysmal nodal tachycardia is presented.

REFERENCES

1. Weiss, S., and Hatcher, R.: Studies on Quinidine, *J. Pharmacol. & Exper. Therap.* **30**: 335, 1927.
2. Weisman, S. A.: Further Studies in the Use of Quinidine in the Treatment of Cardiac Irregularities, *Minnesota Med.* **22**: 285, 1939.
3. Weisman, S. A.: Studies on the Time Required for the Elimination of Quinidine From the Heart and Other Organs, *AM. HEART J.* **20**: 21, 1940.
4. Brodie, B. B., and Udenfriend, S.: The Estimation of Quinine in Human Plasma With a Note on the Estimation of Quinidine, *J. Pharmacol. & Exper. Therap.* **78**: 154, 1943.
5. Hiatt, E. P.: Plasma Concentration Following the Oral Administration of Single Doses of the Principal Alkaloids of Cinchona Bark, *J. Pharmacol. & Exper. Therap.* **81**: 160, 1944.
6. Brodie, B. B., and Udenfriend, S.: The Estimation of Basic Organic Compounds and a Technique for the Appraisal of Specificity, *J. Biol. Chem.* **158**: 705, 1945.

*The occurrence of attacks in G. B. when both daily dose and the interval between successive doses was frequently varied is indicated in the first portion of Fig. 4. All the plasma levels were taken from three to four hours after the preceding dose and probably represented the peak concentrations attained on these schedules. Since there were undoubtedly much lower concentrations at six, eight, and twelve hours, the attacks may have resulted from these lower levels. Therefore, a four-hour schedule was initiated to prevent such wide fluctuations in plasma concentrations.

THE EFFECTS OF THE INGESTION OF LARGE AMOUNTS OF SODIUM CHLORIDE ON THE ARTERIAL AND VENOUS PRESSURES OF NORMAL SUBJECTS

HAROLD GRANT, M.D., AND FRANCIS REISCHSMAN, M.D.
DALLAS, TEXAS

UNTIL recently the most widely accepted explanation of the pathogenesis of edema in acute glomerulonephritis was that, due to an increase in the capillary permeability throughout the body, there was an increased amount of transudation of fluid into the extracellular space. The evidence to substantiate this view was contained in the work of Beckmann,¹ who showed that the edema fluid in four patients with acute glomerulonephritis contained an increased amount of protein. These protein determinations were done by means of a refractometer. Recently, Warren and Stead,¹² using a much more accurate method, found no increase in the protein content of the edema fluid in ten patients with acute glomerulonephritis. Thus, increased capillary permeability could not have been a factor in the production of edema in these patients and another explanation will have to be given.

In 1944 LaDue² made several very interesting observations in twelve patients with acute glomerulonephritis. He found edema, increased venous pressure, and cardiac dilatation in all of the twelve and interpreted these changes as being due to congestive heart failure most likely caused by the arterial hypertension. The question has arisen whether the picture presented by these patients is due to cardiac failure or is due to the abnormal retention of salt and water by the damaged kidneys. The question of the relationship of the salt intake to the level of arterial blood pressure will also be considered.

Grollman and co-workers⁶ have shown that in certain cases of hypertension very rigid restriction of the sodium intake will cause a fall in blood pressure. However, Grollman, Harrison and Williams⁷ demonstrated that an increase in the intake of sodium by hypertensive rats did not cause any further rise in arterial pressure.

In this study the effects of the ingestion of an excess amount of sodium chloride in normal adults was observed.

The subjects used were eight healthy medical students and physicians ranging in age from 18 to 31 years. They were permitted to continue their normal activities throughout the course of the experiment. After a control period of two to four days, the administration of 20 to 30 Gm. of sodium chloride per day, taken in the form of 1.0 Gm. enteric-coated tablets divided into four or five approximately equal doses, was started. No attempt was made to regulate the salt intake in the diet and fluids were allowed ad libitum.

From the Department of Medicine, Southwestern Medical College, and Parkland Hospital.
Aided by a grant from the Daylan Foundation and the John and Mary R. Markle Foundation.
Received for publication April 27, 1946.

TABLE I. CHANGES THAT FOLLOWED THE INGESTION OF LARGE AMOUNTS OF SODIUM CHLORIDE (FIRST THREE SUBJECTS)

DATE	WEIGHT (KG.)	VENOUS PRESSURE (MM. H ₂ O)	FLUID		URINARY CHLORIDES (24 HR.)	SERUM CHLORIDES (MEQ./L.)	BLOOD PRESSURE	REMARKS
			INTAKE (C.C.)	OUTPUT (C.C.)				
H. G. 2/27 2/28 3/1 3/2 3/3	58.25	60					107/70	
	58.50	75					104/62	
	58.75	79					107/67	20 Gm. NaCl q. d.
	58.75	—					106/66	
	58.75	125					110/68	
F. R. 2/27 2/28 3/1 3/2 3/3 3/4 3/5	68.25	88					110/64	
	68.50	86					106/68	
	68.50	88					120/77	20 Gm. NaCl q. d.
	68.75	—					106/66	
	69.25	123					117/74	
	68.85	130					106/66	
D. B. 6/25 6/26 6/27 6/28 6/29 6/30 7/1 7/2 7/3	69.50	150					110/64	
	70.75	146	4,000	1,190	6,610	106.2	116/72	30 Gm. NaCl 30 Gm. NaCl 30 Gm. NaCl
	71.00	170	4,620	1,465	7,250		110/70	
	70.50	138	4,500	1,355	3,150		108/72	
	71.00	164	3,550	2,310	5,280	112.5	—	
	72.25	—	4,450	2,660	21,920		115/70	
	71.50	175	4,310	2,930	33,480			
	71.75	290	3,450	2,530	20,920			
	71.25	—	2,480	1,870	17,350			
	71.50	—	3,300	2,330	17,720			

TABLE II. COURSES THAT FOLLOWED THE INGESTION OF LARGE AMOUNTS OF SODIUM CHLORIDE (LAST FIVE SUBJECTS)

DATE	WEIGHT (KG.)	VENOUS PRESSURE (MM. H ₂ O)	BLOOD VOLUME (C.C.)	PLASMA VOLUME (C.C.)	THIO- CYANATE SPACE (C.C.)	HEMA- TOCRITE	PLASMA PROTEIN	PLASMA CHLORIDES (MEG./L.)	24-HR. URINARY CHLORIDE --GM. (AS NaCl)	FLUID		BLOOD PRESSURE	REMARKS
										INTAKE (C.C.)	OUTPUT (C.C.)		
J. G.													Control period
6/27	68.50	---							4,710	2,710	685	---	
6/28	68.00	102							4,780	1,760	555	128/76	
6/29	67.50	---							4,350	2,690	520	---	
6/30	67.75	96	4,750	2,580	12,320	43.5	7.4	107.7	2,520	2,780	305	126/68	
7/1	---	---							---	3,440	1,305	---	30 Gm. NaCl
7/2	69.80	162							16,400	2,860	1,370	128/76	30 Gm. NaCl
7/3	68.90	154	5,470	3,280	13,900	40.0	7.4	111.0	20,010	2,140	1,030	122/75	15 Gm. NaCl
7/4	---	---							10,250	1,120	1,175	---	
7/5	68.10	104							8,560	2,310	670	---	
W. H.													
6/28	62.50	---								2,915	1,050	---	
6/29	62.50	98								---	---	110/74	
6/30	62.50	113	4,630	2,730	12,790	41.0	7.8	110.4		2,140	730	110/70	
7/1	63.40	---								3,360	1,020	---	30 Gm. NaCl
7/2	63.40	158								---	---	112/70	30 Gm. NaCl
7/3	---	134	5,460	3,380	15,280	38.0	7.6	111.9		---	---	120/70	15 Gm. NaCl
N. K.													
7/11	70.10	108	4,270	2,520	14,270	41.0	7.8	106.8	12,370	2,185	1,190	110/70	25 Gm. NaCl
7/12	68.90	---							11,550	2,210	1,820	114/70	30 Gm. NaCl
7/13	70.00	108							13,830	2,635	1,785	---	30 Gm. NaCl
7/14	70.30	126							21,690	3,540	1,765	110/66	15 Gm. NaCl
7/15	70.90	132							24,230	4,160	1,260	110/70	30 Gm. NaCl
7/16	71.30	138							24,580	3,110	1,580	112/70	30 Gm. NaCl
7/17	72.30	170	4,920	3,150	15,340	36.0	7.4	126.9	24,300	3,360	1,585	118/80	15 Gm. NaCl

7/18	71.40	—							10.640	2,185	2,035		
7/19	71.30	—							3.430	2,760	830		
7/20	70.90	—							10.860	2,190	1,250		
J. H.													
7/13	69.25	125							7.73	2,690	1,050	128/76	
7/14	70.40	—							7.46	3,040	1,150	116/72	
7/15	70.00	105							8.58	2,230	900		
7/16	70.25	133							13.14	3,040	1,250	114/70	20 Gm. NaCl
7/17	69.80	149							25.27	2,245	1,350	116/70	25 Gm. NaCl
7/18	69.80	150						100.8	17.74	2,490	950	130/74	12 Gm. NaCl
7/19	69.40	—							16.79	2,600	1,025		
7/20	69.00	—							10.99	3,380	900		
7/21	68.30	—							7.30	3,670	825		
7/22	—	—							8.18	2,070	730		
B. L.													
7/23	80.3	132											
7/24	80.5	—						108.0		4,150	700	112/78	
7/25	80.4	132								4,930	895	122/82	
7/26	80.5									4,060	675		
7/27	81.6	195								7,070	905	118/82	25 Gm. NaCl
7/28	82.0	193						110.7		5,350	1,746	118/90	25 Gm. NaCl
7/29	81.1									3,140	1,805		12 Gm. NaCl
7/30	78.8									2,210	875		
7/31	80.5									4,420	875	112/78	
										4,850	840		

All subjects were weighed every day at the same time in the postadsorptive state. Venous pressure was determined by the direct method after a rest period of approximately thirty minutes. At the same time, pulse rate and arterial blood pressure were recorded. In five of the subjects additional studies of the changes in body fluids were made. The daily fluid intake and urine output were measured. Blood volume determinations were carried out by the dye method, using T-1824.^{3,4} The ampoules containing an accurately measured amount of dye, as devised by Gregersen,⁴ were used. A period of ten minutes was allowed for mixing, and five samples were taken at ten-minute intervals in heparin-wet syringes. Simultaneously, changes in the volume of extracellular fluid were estimated by measuring the "thiocyanate space" according to the method of Crandall and Anderson,² employing the following formula⁵:

$$\text{"Available fluid"} = \frac{\text{CNS injected (mg.)} \times 100}{\text{CNS in blood (mg. \%)}}$$

Fifty minutes were allowed for mixing and all measurements were done in duplicate. The plasma chlorides were calculated by the titration method. Determinations of the hematocrit and of the total serum proteins were made. In three of these subjects, the twenty-four hour urinary chloride output was measured.

The data obtained are presented in Tables I and II. The first two subjects in Table I (H. G. and F. R.) took sodium chloride for a period of two weeks, but since no essential change in the weight nor venous pressure was noted after the fourth day, the subsequent subjects were given salt for three or four days only.

TABLE III. CHANGES OBSERVED DURING THE PERIOD OF HIGH SODIUM INTAKE

SUBJECT	WEIGHT (KG.)	VENOUS PRESSURE (MM. H ₂ O)	PLASMA VOLUME (C.C.)	R. B. C. VOLUME (C.C.)	BLOOD VOLUME (C.C.)	THIOCYANATE SPACE (C.C.)	PLASMA CHLORIDE (MG.)
H. G.	+0.25	+50					
F. R.	+1.00	+64					
D. B.	+0.75	+126					
I. G.	+1.15	+58	+700	+200	+900	+1580	+3.3
W. H.	+0.90	+21	+650	+180	+830	+2490	+1.5
N. K.	+2.20	+62	+630	+20	+650	+1070	+20.1
J. H.	+0.55	+25	+70	-390	-320	+3260	—
B. L.	+1.50	+61	+430	-20	+410	+1550	+2.7

In Table III are listed the changes which took place during the high sodium chloride intake. In the five subjects on whom more complete circulatory measurements were made, changes were calculated from the data on those days on which the blood volumes were determined. In the remaining three subjects, the last day of the control period and the day of the maximal change in venous pressure were taken for comparison.

All of the subjects showed a gain in weight which varied from 0.25 to 2.20 kilograms. Changes in the venous pressure from +21 to +126 mm. of water

were observed.* Changes in the plasma volume were from + 70 to + 700 c.c.; in the blood volume from -320 to +900 c.c.; and in the "thiocyanate space," from +1,070 to +3,260 cubic centimeters. There were no significant alterations in the arterial blood pressure. The changes observed are presented in graphic form in Fig. 1.

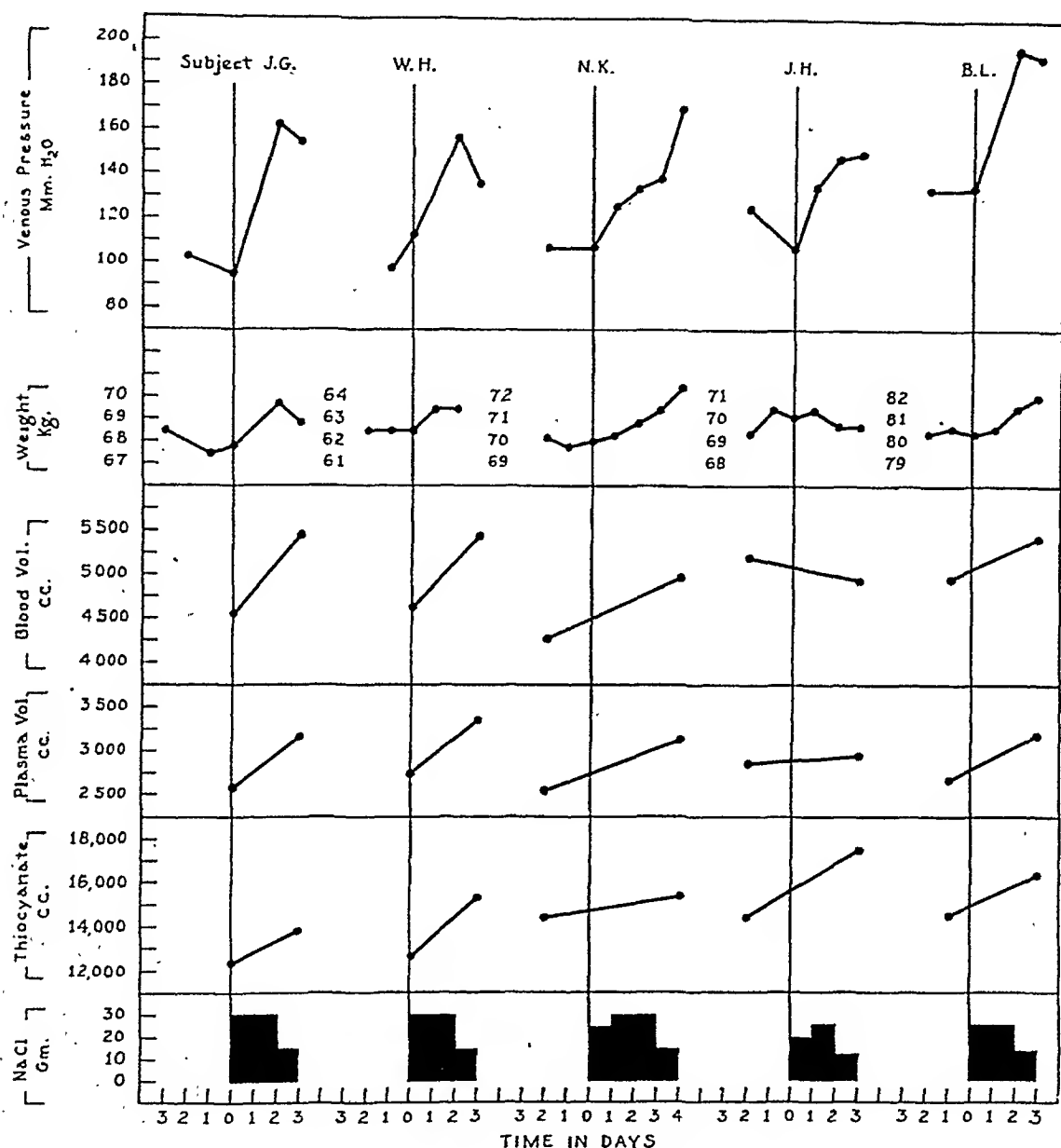


Fig. 1.—Effects of ingestion of sodium chloride.

The variation in venous pressure during the period between two doses of salt was studied. In the first experiment venous pressure curves were done with the subjects (F. R. and H. G.) in a recumbent position. After the administration of salt for several days, each subject took 6 Gm. of sodium chloride and 660 c.c.

*The rise of 126 mm. was observed in subject D. B., an apparently healthy medical student. The control readings ranged from 138 to 170 mm. of water. His past history was negative with regard to cardiovascular and renal disease; findings on physical examination were normal, and teleroentgenography and fluoroscopy of the heart and great vessels revealed no abnormal findings. Urine analysis and Fishberg concentration test were normal.

of water by mouth, and venous pressure readings were taken at frequent intervals through a needle which was left in place and kept patent by a 5 per cent glucose drip at the rate of 15 drops a minute. The same experiment was later repeated but with the subjects ambulatory between venous pressure readings done by multiple venepunctures. The results are presented in Fig. 2. There was a striking difference in the behavior of the venous pressure in the two experiments.

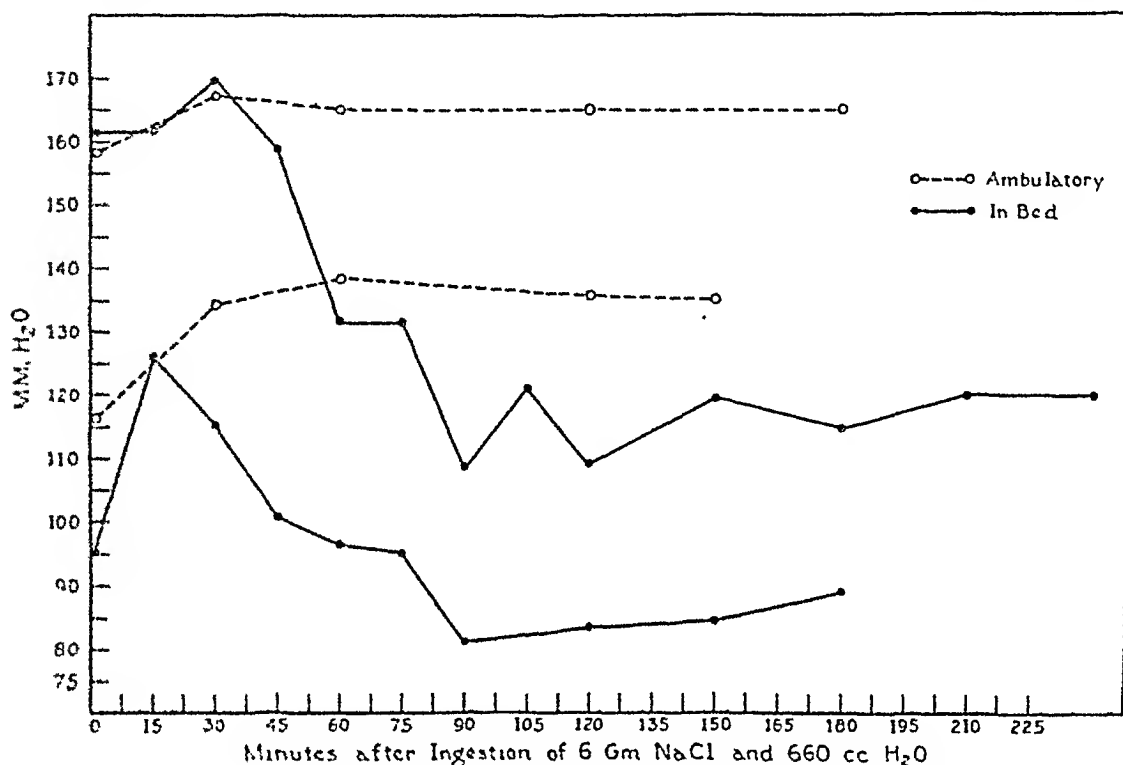


Fig. 2.—Venous pressure curves after single oral dose of sodium chloride during high salt intake.

With the subjects recumbent there was a short initial rise followed by a sustained drop to a level below the initial reading, and both subjects had a diuresis throughout the experiment of approximately 1,200 c.c. each. If the subject remained ambulatory between venepunctures, the initial rise in venous pressure was well sustained and diuresis did not occur.

None of the eight subjects showed a significant change in arterial blood pressure as a result of the increased intake of sodium chloride.

DISCUSSION

A very similar experiment to that reported here was carried out by Lyons, Jacobson, and Avery.¹¹ In seven subjects, after taking 40 Gm. of sodium chloride in forty eight hours, the average weight gain was 1.9 kg. and the average rise in venous pressure, 31 millimeters. These results are quite similar to those observed in this experiment where the average weight gain was 1.04 kg. and the average rise in venous pressure, 59 millimeters. The amount of salt was greater and the duration of observation longer in this present study.

It is evident that when a normal person ingests an excess of sodium chloride and remains ambulatory, the kidneys do not excrete it all, and the isotonicity

of the body fluids is maintained by a retention of water and a subsequent increase in the blood volume and volume of extracellular fluid. The change in plasma protein is much less than the expected fall due to the increase in plasma volume, as noted also by Lyons, Jacobson and Avery.¹¹ This is evidently due to quick mobilization of plasma proteins from storage depots, so that there is actually an increase in the total circulating protein. This rise helps maintain an increased blood volume and the higher venous pressure observed.

In patients with acute glomerulonephritis, during the development of edema there is oliguria and, perhaps, anuria. The question as to which is primary, the edema or the oliguria, remains to be answered. In the twelve patients reported on by LaDue,⁹ all had edema, increased venous pressure, and cardiac dilatation. He interpreted these changes as being due to congestive heart failure brought on by the acute hypertension. However, all of his patients had normal or fast arm-to-tongue circulation times, and the dyspnea and orthopnea were not as prominent symptoms as would be expected if the heart failure were caused by hypertension. It is quite possible that the changes observed in some patients with acute glomerulonephritis are related to the changes seen in normal subjects who are fed an excess of sodium. The latter group showed an increased blood volume, increased extracellular fluid, and a rise in venous pressure.

There have been very few observations on the blood volume in acute glomerulonephritis. The most extensive series was reported by Litzner,¹⁰ who measured the blood volume by use of a dye method in six patients with acute glomerulonephritis while edema was present and again after diuresis. All of these patients showed an increased blood volume which then fell to normal levels when they became free of edema. Calculations of the heart volume were made in five of these patients and all had cardiac dilatation which disappeared when the blood volume became normal. Harris and Gibson⁸ reported the blood volume of four patients with acute glomerulonephritis but did not mention the presence or absence of edema. Only one determination was done and the result compared with expected blood volume as calculated from the patient's height. Two of their patients were found to have normal blood volumes. The other two showed blood volumes which were low, but both of these patients had plasma albumin levels which were very low.

We have recently observed two cases of acute glomerulonephritis. Both of these patients had high venous pressures while edema was present; after diuresis the venous pressure returned to normal levels. However, the fall in blood volume in both of these patients after the edema had disappeared was rather small: 100 c.c. in one instance and 200 c.c. in the other. Neither patient complained of dyspnea nor orthopnea.

In acute glomerulonephritis there is an oliguria which at least in some patients may be due to the pathologic changes in the kidneys. Water and salt are retained, with a subsequent rise in blood volume, venous pressure, and volume of extracellular fluid. The increase in heart size in these patients may be due to the increase in blood volume and venous pressure and greater diastolic filling. That true congestive failure with pulmonary congestion, gallop rhythm, and pro-

longed circulation time occurs in some cases of acute glomerulonephritis is not denied. However, in those patients who do not show pulmonary congestion, gallop rhythm, nor prolonged circulation time, it seems not unlikely that the abnormal degree of hydration observed in acute glomerulonephritis is, for the most part, caused by the retention of salt and water by the diseased kidneys rather than by cardiac decompensation. Up to the present time, blood volume studies have not given convincing evidence for this hypothesis.

As has already been observed in rats,⁷ an increase in the intake of sodium, at least in the doses indicated, does not cause any significant change in the arterial blood pressure.

CONCLUSIONS

1. Normal adults show an abnormal state of hydration when fed an excess of sodium chloride. This state is characterized by an increase in blood volume, venous pressure, and volume of extracellular fluid and may closely simulate the phenomena observed in congestive heart failure.

2. It is suggested that the edema in those patients with acute glomerulonephritis who do not exhibit pulmonary congestion, gallop rhythm, nor prolonged circulation time is caused by the retention of salt and water by the diseased kidneys. This also leads to an abnormally high degree of hydration in which there is increased blood volume, venous pressure, and volume of extracellular fluid.

3. The addition of 20 to 30 Gm. of sodium chloride daily to the diet of normal adults does not cause any significant change in the arterial blood pressure.

The authors wish to express their appreciation to Dr. Tinsley R. Harrison for his help and guidance in this study.

REFERENCES

1. Berkman, K.: Edema, *Deutsches Arch. f. klin. Med.* 135: 39, 1921.
2. Crandall, L. A., Jr., and Anderson, M. X.: Estimation of the State of Hydration of the Body by the Amount of Water Available for the Solution of Sodium thiocyanate, *Am. J. Digest. Dis. & Nutrition* 1: 126, 1934.
3. Gibson, J. G., Jr., and Evelyn, K. A.: Clinical Studies of Blood Volume; Adaptation of Method to Photoelectric Colorimeter, *J. Clin. Investigation* 17: 153, 1938.
4. Gregersen, M. I.: Practical Method for Determination of Blood Volume With Dye T 1824; Survey of Present Basis of Dye-Method and Its Clinical Applications, *J. Lab. & Clin. Med.* 29: 1266, 1944.
5. Gregersen, M. I., and Stewart, J. D.: Simultaneous Determinations of the Plasma Volume With T 1824 and the "Available Fluid" Volume With Sodium Thiocyanate, *Am. J. Physiol.* 125: 142, 1939.
6. Grollman, A., Harrison, T. R., Mason, M. F., Baxter, J., Crampson, J., and Reichsman, F.: Sodium Restriction in the Diet for Hypertension, *J. A. M. A.* 129: 533, 1945.
7. Grollman, A., Harrison, T. R., and Williams, J. R., Jr.: Therapeutics of Experimental Hypertension, *J. Pharmacol. & Exper. Therap.* 69: 76, 1940.
8. Harris, A. W., and Gibson, J. G., Jr.: Clinical Studies of Blood Volume; Changes in Blood Volume in Bright's Disease With and Without Edema, Renal Insufficiency, or Congestive Heart Failure, and in Hypertension, *J. Clin. Investigation* 18: 527, 1939.
9. LaDue, J. S.: The Role of Congestive Heart Failure in the Production of the Edema of Acute Glomerulonephritis, *Ann. Int. Med.* 20: 405, 1944.
10. Litner, S.: Experimentelle und klinische Untersuchungen über das Verhalten der Blutmenge bei Nierenerkrankungen, *Ztschr. f. klin. Med.* 112: 93, 1930.
11. Lyons, R. H., Jacobson, S. D., and Avery, N. L.: Increase in the Plasma Volume Following the Administration of Sodium Salts, *Am. J. M. Sc.* 208: 148, 1944.
12. Warren, J. V., and Strahl, E. A., Jr.: The Protein Content of Edema Fluid in Patients With Acute Glomerulonephritis, *Am. J. M. Sc.* 208: 618, 1944.

ELECTROCARDIOGRAPHIC PATTERNS IN PENETRATING WOUNDS OF THE HEART

PAUL H. NOTH, M.D.
DETROIT, MICH.

INTRODUCTION

INTERPRETATION of the electrocardiographic patterns following penetrating wounds of the heart is both interesting and difficult because of the several factors which may influence the electrocardiogram. The first of these is the localized myocardial lesion produced by the wound itself. Its electrocardiographic effects might be expected to be unique since there is no exactly comparable lesion in the various diseases of the heart. Pathologically it resembles myocardial infarction more than anything else but may be much smaller, usually occurs in an otherwise normal heart, and often involves the right ventricle which is rarely affected in myocardial infarction. A second factor which is practically always present is pericarditis. The mere opening of the pericardium at operation or the presence of blood or of infection in the pericardial sac may cause pericarditis. In contrast to the unpredictable effects of the wound, the patterns produced by pericarditis are quite characteristic, particularly in the acute stage. However, even recently these effects have been attributed mistakenly to the wound itself, and the role of pericarditis has not been recognized. A third factor which is present in some cases is an area of myocardial infarction due to laceration or ligation of a sizeable coronary artery, nearly always the descending branch of the left coronary artery. The combined electrocardiographic effects of the second and third factors are paralleled in previously reported instances of clinical myocardial infarction complicated by pericarditis¹ and experimental myocardial infarction.²

In addition, several other attendant conditions may influence the electrocardiogram. These are shock, anemia, changes in the position of the heart due to air or fluid in the pleural spaces, and, rarely, the coincidental presence of chronic cardiac disease. With the exception of the last condition, these effects are nearly always transient and of insufficient extent to cause confusion in the interpretation of serial tracings.

The possibility of recognizing the changes due to individual factors in these combined patterns has an important bearing upon certain questions about which there has been a diversity of opinion. The fundamental and most difficult of these is whether the wound produces characteristic changes and so may be recognized and located from the electrocardiogram. The question of whether injury

From the Department of Medicine of Wayne University College of Medicine and Detroit Receiving Hospital. Parts of the material in this study have been published in the *Proceedings of the American Federation for Clinical Research* **1**: 49, 1944, and in the *Proceedings of the Central Society for Clinical Research* **17**: 52, 1944, and **18**: 34, 1945.

Received for publication May 13, 1946.

to major branches of the coronary arteries with resultant myocardial infarction becomes apparent in the electrocardiogram is a part of the consideration of localizing findings in such cases. The second question is how often and at what stages the effects of pericarditis appear. Upon the answers to these questions depend certain practical decisions such as the diagnostic value of the electrocardiogram during the preoperative or early period and its subsequent usefulness as a guide to therapy and prognosis. Furthermore, these electrocardiographic effects are of considerable theoretic interest, particularly those following wounds of the right ventricle.

The purpose of this report is to offer a brief analytic review of the literature, some of which is not generally available, to present the electrocardiographic findings in a group of twenty-three patients, and to correlate these with the results of clinical observations in eight patients re-examined after an average period of nineteen months following the cardiac wound.

REVIEW AND ANALYSIS OF THE LITERATURE

GENERAL SCOPE AND CONTENT.—The electrocardiographic changes following wounds of the heart are described in slightly over one hundred cases in the literature available to me. Fifty articles contain reports of single cases.³⁻⁵² Thirty cases are included in the article by Herve and Forero Sarabia.⁵³ McGuire and McGrath⁵⁴ describe the findings in eleven cases, in one of which the electrocardiograms are published. The remaining cases appear in groups of from two to four.⁵⁵⁻⁶¹ There are five articles^{19,31,48,56,65} containing reviews of cases, of which that of Solovay and co-workers,⁵¹ listing the electrocardiographic findings in seventeen cases, is the most extensive.

From the standpoint of analysis of the findings, the seventy cases^{3-35,63,65} in which the electrocardiograms are satisfactorily reproduced are the most valuable ones. However, the studies in many of these cases are incomplete in one or more respects. In twenty-two only one electrocardiogram is recorded. In thirteen the early changes do not appear since the first electrocardiogram was not taken until after the first week. Precordial leads were taken in only twenty-two, and in all of these only a single precordial lead was employed. The most outstanding lack is the paucity of long-term studies. Whereas thirty-one cases were followed for three months or longer, only thirteen were followed for more than six months.

THE ROLE OF PERICARDITIS.—The first definitive studies of the electrocardiographic changes in pericarditis of various etiologic types appeared in 1929.⁶⁶ In 1934 the pathogenesis and evolution of the complete series of changes during both acute and subacute stages were greatly amplified.⁶⁷ It is now well known that pericarditis in both the acute and subacute stages produces electrocardiographic changes which may closely resemble those of myocardial infarction. The first report in the English literature of electrocardiograms following wounds of the heart appeared in 1924,⁸ before the studies just mentioned and during a period of intense interest in the patterns following myocardial infarction. It is apparent, therefore, why these tracings following cardiac wounds were thought to be reflections of the myocardial lesion and why the role of pericarditis was not

appreciated. However, a definite lag is indicated by the fact that since 1930 at least fifteen reports^{6,13,19,21,23,25,28,33,34,40,41,43,51,63,64} have appeared in which interpretations of the electrocardiographic findings were made, but in which the effects of pericarditis are not mentioned. Eight of these have been published since 1938. This oversight has caused a great deal of confusion.

The first mention of pericarditis as a factor in the electrocardiogram following cardiac wounds occurred in the report by Elkin and Phillips⁵⁵ in 1931. The following year Porter and Bigger⁵⁷ felt that they had excluded pericarditis as a factor in their two patients because a pericardial effusion was absent in one and did not parallel the electrocardiographic changes in the other. They based this opinion on the then-prevailing concept that pericarditis produced its electrocardiographic effects only because of generalized myocardial ischemia created by the pressure of the effusion on the heart and coronary vessels. In 1933 Eakin¹¹ and in 1934 Davenport and Markle¹⁰ reported cases in which the tracings were explained in this manner. Schwab and Herrmann³⁰ included a case of a bullet wound of the left ventricle in their studies on the electrocardiogram in pericarditis and first pointed out that the inversion of "coronary" contour of the T waves during the subacute phase of pericarditis was related to the inflammatory process in the subepicardial myocardium. In 1937 Vanderveer and Norris³² stated, "The progressive changes in many cases of stab wounds of the ventricle suggest pericarditis rather than a single anterior lesion of the myocardium." The main thesis in this general article on pericarditis was that their pathologic studies showed that RS-T segment elevations as well as T-wave changes depended upon subepicardial myocarditis and that intrapericardial fluid caused inconstant electrocardiographic changes. Wood⁶⁵ expressed the tentative idea that pericarditis or right ventricular injury accounted for the changes following wounds of the right ventricle, while those following left ventricular wounds were due to the localized myocardial damage. In 1938 the present author⁶⁸ (and later with Barnes⁶⁹), from a review of the published electrocardiograms in cardiac wounds, pointed out the superimposition of changes due to pericarditis upon those due to the wound and, in some cases, also upon the patterns of myocardial infarction from injury of a coronary artery. Winternitz and Langendorf⁵⁸ stated that the electrocardiographic changes following cardiac wounds were most often and most noticeably due to the pericardial reaction and that the direct cardiac injury seldom influenced the electrocardiogram. In 1940 Forero Sarabia⁷⁰ and Parade and Rating⁵⁶ emphasized the prominent part played by pericarditis and its effect in obscuring the changes due to the wound. Solovay and co-workers³¹ in 1941 recognized the preponderant influence of pericarditis during the first two weeks, but after this period ascribed the inversions of the T waves to the myocardial injury.

In 1943 Herve and Forero Sarabia⁵³ drew practically the same conclusions. Their description of the incidence and the types of early changes due to pericarditis agrees so well with other cases in the literature that it serves adequately as a summary of these effects of pericarditis. They found that electrocardiographic evidences of pericarditis were present in twenty-seven of their thirty

patients. The elevated, concave RS-T segments occurred at variable periods. They were present during the first six hours postoperatively in four of nine patients. During the six- to twenty-four hour period they were found in nine of ten patients. After the eighth day the frequency of elevation of the RS-T segments lessened progressively, and they became isoelectric and convex in contour. The T waves, previously upright and often exaggerated in the leads in which elevation of the RS-T segments had occurred, became flattened and then inverted, beginning at the end of the first week and continuing during the second week. At the end of this period 85 per cent of their records showed negative T waves in some or in all of the leads in which they were previously positive. The inversion of the T waves occasionally appeared first in the precordial lead but usually occurred more or less simultaneously in all leads.

Other authors also,^{4,10,12,13,21,35,38,52,51} especially in recent years, have mentioned the role of pericarditis.

LOCALIZING FINDINGS.—

General Review of the Literature.—In 1935 Koucky and Milles¹⁹ stated: "From the standpoint of the electrocardiographic changes resulting from wounds on the anterior surface of the heart, the picture varies but little from case to case, regardless of the presence or absence of involvement of the large coronary vessels or of the region of the anterior surface of the ventricle damaged." In 1937 Wood⁶⁵ asserted that if the wound was situated in the anterior part of the left ventricle toward the apex, or if the anterior descending branch of the left coronary artery had been ligated, the electrocardiogram usually showed the "classical T₁ pattern" and therefore was almost certainly directly due to the myocardial injury; if, however, it was situated in the anterior right ventricle, the electrocardiogram conformed to "the T₂ pattern," with early elevation of the RS-T segment, especially in Lead II, with later inversion of the T waves in all three leads. He tentatively explained these latter changes either on the basis of the hemopericardium or possibly as the direct effects of anterior right ventricular injuries.

In 1938 Winternitz and Langendorf⁶⁸ noted that the cardiac wound itself seldom influences the electrocardiogram, although changes due to myocardial infarction are apparent in some patients in whom the coronary arteries are involved. However, since in their opinion normal coronary arteries withstand ligation better than sclerotic ones, they felt that the electrocardiogram shows only whether or not a cardiac or pericardial lesion is present without indicating with certainty its site or whether or not a coronary vessel is involved. In the same year the present author⁶⁵ (and later with Barnes⁶⁹) found that when the reported cases are divided into two groups, those patients with and those without injury to major coronary vessels, certain differences become apparent. Since these cases are included in the present analysis, this point will be amplified later.

In 1940 Forero Sarabia⁷⁰ declared that the electrocardiographic effects of pericarditis "make impossible or hamper a localizing electrocardiographic diagnosis . . . Such a diagnosis is possible only occasionally when the electrocardiogram has been obtained immediately after the surgical intervention or

long enough afterward so that the signs of pericarditis have disappeared." In 1941 several authors commented on the presence or absence of localizing findings. Bean⁴ reported a case of a bullet wound of the heart with ligation of the anterior descending branch of the left coronary artery and recognized changes which he felt were due to the combined effects of pericarditis, operative trauma, and the bullet wound. Q-wave patterns suggesting damage to both anterior and posterior surfaces of the left ventricle were present. Solovay and co-workers,³¹ from a review of the electrocardiograms in seventeen cases, including one case of their own, agreed with Wood's idea as to the existence of a "T₁ pattern" in left ventricular wounds and a "T₂ pattern" in right ventricular wounds. They felt that inversions of the T waves after two weeks were due to the myocardial injury and therefore could be used in its localization. McGuire and McGrath⁵⁴ stated in a brief report that in their eleven patients, "the electrocardiographic changes were similar whether the right or left ventricle was injured and had no localizing value . . . The electrocardiograms in two patients in whom the anterior coronary artery and vein were ligated were similar during the first week after operation to the records of the other patients." The electrocardiograms of only one patient in their series are published and the other tracings are not described in detail.

The impossibility of evaluating localizing changes when the pattern of pericarditis is not appreciated is illustrated by Caviness and Turner's⁶ report in 1943 of a wound of the left auricle, in which they stated that "electrocardiographic changes incident to injury of the auricles are not essentially different from those caused by injury to other portions of the myocardium such as occur after coronary occlusion." Their series of electrocardiograms showed no changes in the P waves and no Q-wave patterns, whereas the T waves were inverted and "coronary" in contour in the three standard leads—a finding characteristic of pericarditis. Zerbini³⁵ reported on a patient with a right ventricular wound in whom the descending branches of the left coronary artery and vein were ligated about 4 cm. above the apex. He stated that the curves did not reflect myocardial infarction since there was no Q wave in the precordial lead. In the published precordial electrocardiograms the R and S waves are of equal amplitude, probably indicating that the electrode was placed over the antero-septal portion of the left ventricle. This case is of interest since it may be comparable with instances of anterior myocardial infarction in which multiple precordial leads show Q waves in one or a few leads but not in others. Herve and Forero Sarabia⁵³ modified the previously quoted statement of the latter of these two authors by pointing out that the study of localizing patterns permits a general idea of common distinctive characters among different groups, left ventricular wounds generally causing alterations in T waves in Leads I and IV which are more marked and more persistent than the changes in the T waves in Leads II and III. In right ventricular wounds they sometimes found abnormalities of T₁ and T₄ but noted that these changes tended to regress during the second month, whereas the changes in T₂ and T₃ persisted for a longer time. Three of fourteen right ventricular wounds showed either complete or incomplete right bundle branch block. P-wave

changes of questionable extent occurred in two of the five auricular wounds. In all, eleven of twenty-seven patients presented signs definitely suggesting the location of the wound. In many of the remaining patients only one or a few electrocardiograms were taken. Among eleven patients there was frequently a discrepancy between the location described at operation and that found at autopsy. The most common error was to mistake right ventricular for left ventricular wounds. This observation is important because it may explain discrepancies in some cases between localizing electrocardiographic patterns and the supposed location of the wound.

Analysis of Localizing Findings in Electrocardiograms Depicted in the Literature.—There are several inherent difficulties in an analysis of localizing findings in electrocardiograms depicted in the literature. The first of these is that the true incidence of localizing patterns can be only roughly estimated because the electrocardiographic studies are often incomplete in one or more respects. The second is, as pointed out by Herve and Forero Sarabia,⁵³ that the surgeon's description of the location of the wound cannot be relied upon completely. The third is, during a considerable period of time, that the effects of pericarditis may obscure localizing findings. To avoid this last difficulty, it has been suggested that tracings taken either very early or considerably later when these effects have disappeared should be the most valuable. This suggestion has been adopted in the present analysis though with certain reservations which will be mentioned.

Cases With Early Electrocardiograms: Table I shows an interpretation of the findings in thirty-one cases depicted in the literature with tracings taken during the first twenty-four hours. The word localizing has been used thus far to indicate changes pointing to the particular part of the heart involved by the wound. In this sense there are only two patterns which have localizing value at this stage. The first of these is that of myocardial infarction. When this is present, it indicates that the wound is in one or the other ventricle but near enough to the coronary artery, nearly always the anterior descending branch of the left, so that this artery is involved in the wound or during its suture. Among the seven patients in the first group in Table I, this was proved to be present in six and considered very probable in the seventh. In three of these, a definite pattern of anterior infarction consisting of a reciprocal depression of the RS-T segment in Lead III, measuring 2 mm., is present. In three of the other four patients, similar though less deep reciprocal depressions occurred, but because of the fact that in a few instances acute pericarditis may show slight RS-T depressions in Lead III, these three cases are classified as suggestive rather than diagnostic of anterior infarction. One other case is classified as suggestive of infarction because of the presence of a Q wave in Lead I. In only one of these seven patients was a precordial lead obtained during the first twenty-four hours, and in this patient⁴ the Wolferth lead showed a small Q wave which would be equivalent to a small R wave in the precordial leads now in use. The absence of the pattern of infarction in three preoperative tracings is due to the fact that this occurred as a result of ligation of a coronary artery during the operation.

TABLE I. INTERPRETATION OF ELECTROCARDIOGRAPHIC FINDINGS IN THIRTY-ONE CASES DEPICTED IN THE LITERATURE WITH TRACINGS OBTAINED DURING THE FIRST TWENTY-FOUR HOURS

GROUP	NUMBER OF CASES	DEFINITE FINDINGS			SUGGESTIVE FINDINGS			NON-SPECIFIC MYO. DAM.	NORMAL
		INFARCT.	B.B.B.	PERICARD.	INFARCT.	B.B.B.	PERICARD.		
Ventricular wounds with known or probable involvement of the left coronary artery	7	3 (12, 16, 27)			4 (4, 9, 55 (Case 1) 57 (Case 1))		2 (55 (Case 1) 27)	1 (9)	
Right or left ventricular wounds without known involvement of a coronary artery	17		2 (10, 53 (Case 2))	9 (5, 19, 21, 53 (Cases 4, 8, 20, 22) 54 (Case 1) 57 (Case 2))		1 (53 (Case 3))	2 (53 (Cases 3, 21))	3 (53 (Cases 12, 21, 22))	3 (33, 53 (Cases 6, 9))
Wounds of both right and left ventricles	1		1 (17)						
Atrial wounds	4			2 (11, 53 (Case 26))			1 (15)	1 (32 (Case 5))	
Unknown location	2							1 (58 (Case 22))	1 (30 (Case 7))
Totals	31	3	3	11	4	1	5	6	4

Infarct., Infarction; B.B.B., bundle branch block; Pericard., pericarditis; Myo. Dam., myocardial damage. Numbers within parentheses refer to the numerical order of the articles in the list of references. The reference numbers printed in heavy type indicate that the electrocardiographic finding described appeared in a preoperative tracing shown in the article. Dotted lines connect multiple tracings within first twenty-four hours. In three other cases two possible interpretations are listed for each. The total of interpretations thus exceeds the number of cases.

TABLE II. ELECTROCARDIOGRAPHIC FINDINGS AMONG THE TWENTY-THREE CASES WITHOUT LIGATION OF A CORONARY ARTERY FOLLOWED THREE MONTHS OR LONGER DEPICTED IN THE LITERATURE

REFERENCE	NUMBER OF LEADS	TYPE OF FINDING	TIME OF FOLLOW-UP (MONTHS)	NUMBER OF PATIENTS
A. Left Ventricular Wounds (Seven Cases)				
3, 31, 55 (Case 2)	3, 3, 3	Normal electrocardiogram	4, 4, 6	3
53 (Case 17)	3	Inverted T ₁ and T ₂ ; Q ₁	10	1
18	3	Inverted T ₁ ; Q ₁	10	1
3	3	Diphasic T ₁	3	—
21	3	Low T ₁ ; notched QRS	6½	1
53 (Case 22)	4	Low T ₁ ; inverted T ₄	3	1
		Rounded T ₄ ; elevated S-T ₄ ; small R ₄ ; low voltage	7	
B. Right Ventricular Wounds (Twelve Cases)				
14, 19, 20, 33	3, 3, 3	Normal electrocardiogram	3, 4, 4,	6
53 (Case 12), 54 (Case 1)	3, 4, 4		5, 5, 17	
8	3	Right bundle branch block	3	1
53 (Case 14)	4	Right bundle branch block; low T ₁ ; inverted T ₂ , 3, 4; R ₄ > S ₄	4	1
28	3	Diphasic T ₁ ; inverted T ₂ and T ₃	5½	1
54 (Case 1)	4	Inverted T ₂ and T ₃ ; R ₄ > S ₄	3	—
53 (Case 9)	3	Isoelectric T ₂ ; inverted T ₃	3	1
57 (Case 2)	3	Isoelectric T ₁	4	1
31	4	Inverted T ₄ ; ? T ₂ ; inverted T ₃ ; S ₄ > R ₄	5	1
C. Auricular Wounds (Three Cases)				
6	4	Normal electrocardiogram	3	1
11	3	*Isoelectric T ₁ , 2, 3; low voltage	6	1
53 (Case 26)	4	Isoelectric T ₁ , 2, 3; T ₄ low up	3	1
D. Right and Left Ventricle (One Case)				
23	3	Normal electrocardiogram	6	1
E. Total Cases (Twenty-Three)				
		Normal electrocardiogram	5.5 (Av.)	11
		Abnormal electrocardiogram	5.6 (Av.)	12

* Indicates that amplitude of the deflection preceding the sign exceeds that of the deflection following it. The brackets connect cases studied at more than one time after the three-month period.
* Probable chronic pericarditis

The second localizing finding in these early tracings is that of bundle branch block. This was always a right bundle branch block and in all instances, except one in which wounds were present in both ventricles, the right ventricle was the site of the wound. Since, in several other patients reported on in the literature and in two patients in the present series, the right ventricle was always involved by the wound when this pattern was present, it is considered to be of localizing significance.

Other than these two types of localizing patterns, there are no findings at this time which indicate the part of the heart involved. The degree or location of elevations of the RS-T segments or abnormalities of the T waves are not distinctive of a particular location. It is apparent that since definite electrocardiographic evidences of pericarditis are present in eleven patients, pericarditis is capable of obscuring localizing patterns even at this early stage. However, if the word localizing is used in the broader sense of evidence of involvement of any part of the heart, then pericarditis may be considered as a localizing finding. Including it, there are only ten of the thirty-one patients in whom there is neither definite nor suggestive evidence of cardiac or pericardial involvement. Of these ten, six showed nonspecific changes which might be expected to result from shock or anemia, and in four the tracings were within normal limits.

Cases With Late Electrocardiograms: For reasons to be commented upon later it seems desirable to consider only those in which tracings were obtained three months or later following the wound. Table II shows the patterns observed in the twenty-three patients without known coronary involvement. There are five wounds of the left ventricle associated with electrocardiographic abnormalities

TABLE III. ELECTROCARDIOGRAPHIC FINDINGS AMONG THE EIGHT CASES WITH LIGATION OF THE LEFT CORONARY ARTERY OR ITS BRANCHES FOLLOWED THREE MONTHS OR LONGER AND DEPICTED IN THE LITERATURE

REFERENCE	NUMBER OF LEADS	TYPE OF FINDING	TIME OF FOLLOW-UP (MONTHS)	NUMBER OF PATIENTS
<i>A. Left Ventricular Wounds (Three Cases)</i>				
57 (Case 1)	3	Normal electrocardiogram	3	1
12	4	Low T ₁ ; diphasic T ₄ ; small Q ₁ ; R ₄ = S ₄	7	1
9	4	Low T ₁ ; inverted T ₄ ; Q ₄ ; S ₄ > R ₄	6	1
<i>B. Right Ventricular Wounds (Five Cases)</i>				
8, 55 (Case 1)	3	Normal electrocardiogram	3, 8	2
35	4	Inverted T ₄ (R ₄ = S ₄)	8	1
4	4	Isoelectric T ₂ ; inverted T ₄ ; Q ₄	13	1
22	3	RV x-systoles Diphasic T ₁ ; Q ₁ and Q ₂	48	1

x—systoles, extra or premature systoles.

persisting for three months or longer. In one of these the electrocardiogram became normal subsequently. All show involvement of the T wave in Lead I, and only one showed involvement of T₂. On the other hand, four of the five right ventricular wounds with persisting abnormalities other than right bundle Branch Block show altered T waves in Leads II and III, whereas only two show altered T waves in Lead I. The location of the single precordial electrodes in these patients is presumably at the cardiac apex or in the midclavicular line. As judged by the relative amplitudes of the R and S waves, the electrode was most frequently near a point over the interventricular septum where both right and left ventricular events might influence the direction of the T waves.

Table III shows the electrocardiographic findings in eight cases with ligation of the left coronary artery or its branches followed three months or longer and depicted in the literature. The electrocardiogram became normal in three patients, in all of whom there was no precordial lead, whereas it remained abnormal in five patients, in four of whom a precordial lead was taken. Q waves were present in the precordial lead in two patients. In another, a Q pattern occurred in the standard leads. The patterns in left and right ventricular wounds are seen to be more alike, as would be expected if the infarcted area was exerting a preponderant influence.

PRESENT STUDY

MATERIAL AND METHOD.—Electrocardiograms were obtained from twenty-three patients suffering from penetrating cardiac wounds. The number of tracings for each patient varied from one to twenty for each patient but was less than three in only three patients; the average number was seven. In two only the standard limb leads were taken; in five a single precordial lead (IV F) also was obtained on one or more occasions; in four the precordial Leads V₂, V₄, and V₆ were obtained in addition to the standard limb leads; in one there were three standard and six precordial leads (V₁-V₆); in eleven a total of twelve leads (three standard, V₁-V₆, and augmented unipolar leads from the extremities) were taken on one or more occasions. Of the twenty-one patients with one or more precordial leads, these were first recorded during the first week following the wound in six, during the second week in five, during the third week in four, and after this in the remaining six.

The first electrocardiogram was taken preoperatively in two patients, during the first day in six, during the second day in five, during the third day in six, during the fourth day in one, during the fifth day in two, and on the thirteenth day in one.

In nineteen patients the period of electrocardiographic study varied between eighteen days and three years. In five, this period was one month or less; in two, it terminated during the second month; in twelve it extended for three months or longer. Five patients in this last group had electrocardiograms over a period of from two to three years.

Eight patients were completely re-examined by me at periods varying between five and thirty-six months, averaging nineteen and one-half months, following the wound. Ten patients had follow-up roentgenologic studies.

The location of the wound was determined at operation in eighteen patients. In five it was in the right ventricle; in eleven, in the left ventricle; in one, in the left auricle; and in one it involved only the pericardium and a branch of the right pulmonary vein. In the five patients in whom operation was not performed, cardiac involvement was indicated in three by the presence of physical signs of cardiac tamponade, the fluoroscopic findings of an enlarged nonpulsating cardiac shadow, and the aspiration of blood from the pericardial sac. In the other two patients (Cases 19 and 20) these signs were not described, and the diagnosis of cardiac involvement was based chiefly on the electrocardiogram.

These cases are included in a study on the surgical aspects of penetrating cardiac wounds by Blau.⁷²

FINDINGS.—

General Findings.—Table IV shows the evolution of the principal electrocardiographic changes and their interpretation in terms of the presence or absence of pericarditis, nonspecific myocardial damage, and localized myocardial damage resulting from the wound. The electrocardiograms returned to normal in six patients. The time of the normal tracing varied between ninety-five days and thirty-three months, averaging fifteen and one-half months. However, the time of the last preceding abnormal tracing averaged only forty-two days, indicating that there was usually a long period between these abnormal and the subsequent normal tracings. Therefore, these cases do not provide information as to the length of time actually required for the return to normal. Follow-up on the six patients with persistently abnormal electrocardiograms (Table V) was continued for an average period of twenty-one months, which is longer than the follow-up on the group of patients with a return to normal, so that it can be stated that the length of the follow-up period does not account for the differences between these two groups.

Definite evidences of pericarditis are present in seventeen patients. In seven of these (Cases 7, 9, 11, 16, 17, 22, and 23) no other abnormalities can be detected. Five others (Cases 5, 6, 14, 15, and 19) showed changes suggestive of pericarditis. The only one (Case 20) in whom no electrocardiographic evidence of pericarditis appeared is the patient in whom the first electrocardiogram was not taken until the thirteenth day, and the presence of anterior left ventricular damage makes it impossible to interpret the inversions of the T waves on any other basis, even though pericarditis may be a factor.

Patterns attributable to the wound and therefore of localizing value are definitely present in ten patients (Cases 1, 5, 6, 8, 10, 13, 14, 15, 19, and 20), questionably present in five (Cases 3, 4, 12, 18, 21), and absent in the remaining eight cases. There are ten patients (Cases 1, 2, 4, 6, 8, 9, 13, 14, 20 and 21) in whom, in addition to patterns of pericarditis and/or localized myocardial damage from the wound, various changes appeared which are classified as evidences of nonspecific myocardial damage. They include depression of the R-T segment in one or more leads (three cases), inversion of T waves during the first week in leads other than those reflecting the localized myocardial damage (three cases),

TABLE IV. EVOLUTION OF PRINCIPAL ELECTROCARDIOGRAPHIC FEATURES

CASE	LOCATION AND DEPTH OF LESION	PRE-OPERATIVE	FIRST DAY	2-7 DAYS	SECOND WEEK	THIRD WEEK	FOURTH WEEK	SECOND MONTH	THIRD MONTH	SUBSEQUENT	INTERPRETATION
1. R. H. 41-42; 48 yr. C. M. (Fig. 3)	R.V. (near apex, 2.0 cm.); stab			R-T _{1,2} , elev.; R-T ₃ , sl. dep.; T _{1,2} , diph.; T ₃ , neg.; aur. fibrill.; L.A.D.	R-T _{1,2} , iso.; R-T ₃ , sl. dep.; T _{1,2} , dome; T ₃ , neg.; sinus rhythm					35th mo.: L.A.D.; L.V.P.; def. i.v. cond. (inc. right B.B.B.); T _{1,2,3} , diph.; T _{3,4} , inv.; S _{v4} > R _{v4} ; R.V. x-systoles	Early, pericarditis and myocardial damage; later, local damage R.V., from wound; nonspecific damage indicated by early diaphasic T _{1,2} ; aur. fibrill.
2. A. J. 43-46; 32 yr. C. M. (Fig. 2)	R.V. (middle, 1.3 cm.); stab			R-T _{1,2} , elev.; T _{1,2} , diph.; T ₃ , neg.	R-T _{1,2} , elev.; T _{1,2} , up; T ₃ , sl. neg.	R-T ₃ , iso.; T ₁ , T ₂ , 6, diph.; T _{v4} , neg. (v ₄ taken over L.V.)	T _{1,2,3} , diph.; T _{v2,4,6} , neg.				Early, pericarditis and myocardial damage; later, pericarditis and ? local myocardial damage
3. L. J. 41-43; 54 yr. C. M. (Fig. 4)	R.V. (small); stab			R-T _{1,2} , elev.; T _{1,2} , up; T ₃ , neg.; occasional R.V. x-systole	R-T _{1,2,3} , iso.; T ₁ , diph.; T _{2,3} , neg.		T ₁ , T _{v6} , iso.; T _{2,3} , neg.; T _{v4} , diph. (S _{v4} > R _{v4}); T _{v2} , up	T ₁ , low up; T _{2,3} , neg.; T _{v2,4,6} , up		95th day: Normal ECG	Early, pericarditis; (later, pericarditis and ? T ₂ -T ₃ pattern of R.V. damage
4. H. S. 41-47; 30 yr. C. M.	R.V. (upper); stab			R-T _{1,2} , elev.; R-T ₃ , sl. dep.; T _{1,2} , up; peaked; T ₃ , neg.; defective i.v. conduction	R-T _{1,2,3} , 6 sl. dep.; R-T ₃ , elev.; T _{1,2,4,6} , neg. (R _{v4} > S _{v4}); T ₃ , low, up		R-T, iso.; T ₂ , diph.; T ₁ , v ₁ , v ₆ , neg.; QRS volt., lower, borderline in stand. leads			33rd mo.: normal ECG	Early, pericarditis, ? local subpericardial R.V. effect causing elev. R-T _{v2} (4 mm.); early nonspecific myocardial damage (defective i.v. conduction)
5. G. G. 44-45; 33 yr. C. M. (Fig. 3)	R.V. (middle, large; near apex; smaller); stab			Incomplete right B.B.B.; low volt.; R-T _{vav1} , elev.; T _{v1} , neg.; T _{v2,4,6} , diph.; Q _{v1} = 5 mm.							R.V. myocardial damage; ? localized pericarditis causing elev. R-T _{v1,4}

6. G. V., 41-13765; 29 yr. C, M (Fig. 5)	L.V. (near left coronary artery); stab		R-T _{1,2} , sl. elev.; T's, up; low volt.; small Q _{2,3}	R-T _{1,2} , sl. elev.; T's, low up; low volt.; small, Q _{2,3}	T _{1,2} , sharply neg.; T ₃ , diph.; normal volt.; Q _{2,3}	T _{1,2} , neg.; T ₃ , up; prolonged QT; Q _{2,3}	T _{1,2} , neg.; T ₃ , up; T _{V2,3,6} , neg.; R _{V4} , less than 1 mm.; small Q _{2,3}		36h mo.: T ₁ , iso.; T ₂ , T _{V4} , diph.; T _{V5,6} , neg.; diminished R _{V4} ; low volt. stand. leads, Q _{2,3} , Q _{V6}	Early ECG's strongly suggestive of peri- carditis; later, L.V. myocardial damage from wound, possibly infarction prolonged Q-T, a nonspecific change
7. C. D., 42-3530; 30 yr. C, M	L.V. (mid- anterior, small); stab		R-T _{1,2} , elev.; R-T ₃ , sl. dep.; T _{1,2} , up, peaked; T ₃ , neg.	R-T _{1,2,3} , iso.; T _{1,2} , diph.; T ₃ , up		R-T _{1,2,V4,V6} , elev.; R-T ₃ , sl. dep.; T _{1,2,V6} , up; T _{3,V2,V4} , diph.			ECG's show only pericarditis which recurred clinically at 30 days	
8. G. E., 44-110; 33 yr. C, M (Fig. 6)	L.V. (bullet tunnelled lateral L.V. 3 cm. above apex)		R-T _{1,2} , elev.; T ₁ , up; T ₂ , diph.; T ₃ , neg.	R-T ₁ , sl. elev.; R-T _{2,3} , iso.; T _{1,2} , neg.; T ₃ , iso.; P-R = 0.22 sec.	R-T's, iso.; T _{1,2} , more deeply inv.; T ₃ , up; T _{V1-6} , neg.; P-R = 0.24 sec.	T waves all more deeply inv. except T ₃ now, diph. and T _{V1} , up; P-R = 0.24 sec.	T _{1,2,V3-6} , neg.; T ₃ , diph.; T _{V1,2} , up; T invers. sl. less deep.; P-R = 0.20 sec.	8h mo.: T-wave invers. persistent though less marked in 1,2,V3-6; P-R = 0.24 sec.	Early, pericarditis; later (18 days and sub- sequent), L.V. myo- cardial damage; non- specific myocardial damage	
9. O. H., X-6627; 40 yr. C, F	L.V. (30 cm. above apex); stab		Same as 1st day except greater S-T elev., incr. volt., parox. aur. fibrill.						Early stage of peri- carditis; died seventh day, autopsy: purulent pericarditis, non- specific damage indi- cated by auricular fibrillation	
10. E. W., 42-5620; 33 yr. C, M (Fig. 6)	L.V. (1.75 cm. long); stab		R-T _{1,2} , elev.; R-T ₃ , iso.; T _{1,2} , up; T ₃ , iso.; L.A.D.		R-T _{1,2,3} , iso.; convex; T _{1,2,3} , neg.		T _{1,2,3,V6} , neg.; L.A.D. with S ₃ varying with respira- tion	28h mo.: T ₁ , T _{V6} , diph.; T ₂ , T _{V6} , neg.; L.A.D.	Early, pericarditis; left ventricular damage at twenty- eighth month	

Aur. fibrill., auricular fibrillation; A-V, auriculoventricular; B.B.R., bundle branch block; O, colored; def. i.v. cond., defective intraventricular conduction; dep., depressed; diph., diphasic; elev., elevated; F, female; inc., incomplete; incr., increased; inv., inverted; invers., inversion; iso., isoelectric; i.v., intraventricular; L.A., left auricle; L.A.D., left axis deviation; L.V., left ventricle; L.V.P., left ventricular preponderance; M, male; Mo., month; neg., negative; parox. aur. fibrill., paroxysmal auricular fibrillation; p.o., postoperative; Q_{AVF}, Q wave in augmented unipolar lead from left leg; R-T, R-I or RS-T segment; R. V., right ventricular; sl., slightly; S > R, S exceeds R in amplitude; stand., standard; S-T, R-T or RS-T segment; T's, T waves; volt., voltage; W, white; x-systoles, extra- or premature systoles.

TABLE IV. EVOLUTION OF PRINCIPAL ELECTROCARDIOGRAPHIC FEATURES—CONT'D

CASE	LOCATION AND DESCRIPTION	PRE-OPERATIVE	FIRST DAY	2-7 DAYS	SECOND WEEK	THIRD WEEK	FOURTH WEEK	SECOND MONTH	THIRD MONTH	SUBSEQUENT	INTERPRETATION
11. R. Q. X-17261; 26 yr. C. M	L.V. (1.0 cm. to left of left coronary artery; 1.0 cm. below A-V junction); stab	R-T _{1,2,3,4} , iso.; T _{1,2,3} , up; T ₃ , diph.; basilar notch; QRS _{1,2,3}	8 hours p.m.: R-T ₁ , elev.; T _{1,2,3} , up; T ₃ , tall, peaked; L.A.D. 2 1/2 hours: R-T _{1,2} , elev.; T _{1,2} , tall, peaked; QRS volt. lower; L.A.D.	R-T ₁ , iso.; R-T ₂ , elev.; T _{1,2,3,4} , up; low volt.; L.A.D.	R-T _{1,2,3} , iso.; T's, up; small Q _{1,2,4}	T _{1,2,3,4} , low and dome shaped; low volt.; L.A.D.	T's same; QRS volt. incr. to normal; L.A.D.				Only pericarditis
12. L. G., 41-568; 21 yr. W. M (Fig. 2)	L.V. (Trans- verse, at junction with L.A.); stab			R-T _{1,2,3} , elev.; T _{1,2} , up, peaked; T ₃ , up; small Q _{1,2,3}	R-T _{1,2,3,4} , elev.; T's, up; small Q _{1,2,4}	R-T's, iso.; T _{1,2} , diph.; T _{2,3} , up; small Q _{1,2,4}	T _{1,2,3,4} , neg.; T ₃ , iso.; small Q _{1,2,3,4}	31 days: T _{1,2,3} , low up; T ₃ , diph. 45 days: T _{1,2} , neg.; T _{2,3} , up; Q's as before	30th mo.: Normal ECG (small Q _{1,2,3} , v _{1,5,6})	Pericarditis; ? "T ₁ pattern" of L.V. injury at 45 days; Q's insignificant; ECG signs of recurrent pericarditis at 31 days	
13. G. C., 43-15198; 33 yr. C. M	L.V. (2.0 cm., anterior, near base); stab	?		R-T ₁ , sl. elev.; R-T _{2,3} , iso.; T _{1,2} , up, peaked; T ₃ , neg.; L.A.D.; borderline volt	R-T _{1,2,3,4} , sl. dep.; R-T ₃ , sl. elev.; R-T _{2,3,4} , iso.; T _{1,2,3,4} , diph.; semi- horizontal position; L.A.D.; borderline volt	R-T ₁ , sl. dep.; R-T ₂ , iso.; R-T ₃ , sl. elev.; T _{1,2} , diph.; T ₃ , neg.; L.A.D.; borderline volt			3 1/2 mo.: T _{1,2,3,4} , low up; T ₃ , diph.; T _{2,3,4} , up; normal volt.; L.A.D. 11 mo.: Normal ECG (12 leads); hori- zontal position of heart; L.A.D.	Pericarditis; diffuse myocardial damage (second week); L.V. myocardial damage (3 1/2 months)	

TABLE IV. EVOLUTION OF PRINCIPAL ELECTROCARDIOGRAPHIC FEATURES—CONT'D

AGE	PATHOLOGY AND DESCRIPTION	PRE-OPERATIVE	FIRST DAY	2-7 DAYS	SECOND WEEK	THIRD WEEK	FOURTH WEEK	SECOND MONTH	THIRD MONTH	SUBSEQUENT	INTERPRETATION
17. O. P. R-1069; 23 yr. C. M. (Fig. 1)	Pulmonary vein and pericardium		Immediate p.o.; R-T _{1,2,3,4} , iso.; T ₁ , low, up; T _{2,3,4} , up; L.A.D. 22 hours: R-T _{1,2,3,4} , elev.; T _{1,2} , up, peaked; T ₃ , neg.; QRS, volt. lower; L.A.D.	R-T _{1,2} , elev.; R-T ₃ , dep.; T _{1,2} , up; T ₃ , neg.; L.A.D.	R-T _{1,2} , sl. elev.; R-T ₃ , iso.; T ₃ as before	R-T ₃ , iso.; arched in 1-2-4, T _{1,2,3,4} , neg.	T _{1,2,3,4} , neg.		T _{1,2} , sl. neg.; T ₃ , low up	97 days: R-T _{1,2,3,4} , elev.; R-T ₃ , ? dep.; T _{1,2,3,4} , up; T ₃ , ? neg.	Pericarditis persistent at 76 days; recurrent acute at 97 days
18. H. P. V-5186; 23 yr. C. M. (Fig. 1)	Left atrium (2.5 cm.); stab		R-T _{1,2} , elev.; R-T ₃ , sl. dep.; T _{1,2,3,4} , up; borderline volt.; P _{1,2} , sl. notch, small	R-T _{1,2,3,4} , elev.; R-T ₃ , iso.; T _{1,2,3,4} , low up; L.A.D., with variable Q ₃ ; normal volt.; P _{1,2} , sl. notch, small	R-T _{1,2,3,4} , elev.; T _{1,2,3,4} , low up; T ₄ , notched; L.A.D. gone; P _{1,2} , sl. notch, small	R-T _{1,2,3,4} , dep.; T _{1,2,3,4} , neg.; sl. L.A.D.; Q ₃ ; P _{1,2} , sl. notch, normal volt.	R-T _{1,2,3,4} , sl. dep.; T _{1,2,3,4} , neg.; deeper; L.A.D. gone; P _{1,2} , sl. notch, lower, duration, approx. 0.11 sec.				Pericarditis; suggestion of atrial damage (left)
19. O. P. 42-45355; 26 yr. C. M. (Fig. 7)	? Stabbed in back with long knife		R-T ₁ , sl. elev.; R-T _{2,3,4,5,6} , iso.; T _{1,2,3,4,5,6} , neg.; Q _{1,5,6} , small; Q _{2,3} , larger	R-T ₁ , sl. elev.; R-T _{2,3,4,5,6} , iso.; T _{1,2,3,4,5,6} , neg.; Q _{1,5,6} , small; Q _{2,3} , larger	R-T ₁ , iso.; T ₁ , low up; Q waves as before	T ₁ , taller; T _{2,3} , deeper; T _{5,6} , neg.; Q _{2,3} , deeper	R-T _{1,2,3,4} , sl. dep.; T _{1,2,3,4} , neg.; deeper; L.A.D. gone; P _{1,2} , sl. notch, lower, duration, approx. 0.11 sec.	T ₁ , normal; T _{2,3} , deeper; T _{5,6} , tall; T _{5,6} , up; small Q _{1,5,6} , deep Q _{2,3}			Probable pericarditis; myocardial damage posterior—basal L. V.; ? wound or infarction from laceration right coronary

20. P. E., X-11784; 27 yr. C, M (Fig. 7)	? Precordial wound 5.0 cm. left third interspace, nipple line; stab			R-T _{1,2} , sl. dep; T _{1,4} , v ₆ , up; T ₂ , v ₂ , up, double; T ₃ , neg.		R-T _{1,2} , sl. dep.; R-T _{1,2,4} , arched; T _{1,2,4,6} , neg.; T ₃ , up; L.A.D. R _{4,6} , absent	Same as second week	T ₁ , less deep; T _{4,6} , deeper; T _{2,3} , neg.; R _{4,6} , absent	Same as fourth week		L.V. myocardial damage; ? wound or infarction from laceration left coronary artery
21. L. Mc., 44-4951; 32 yr. C, F (Fig. 7)	? Several puncture wounds on chest wall from icepick; stab		R-T _{1,2} , sl. dep; T _{1,4} , v ₆ , up; T ₂ , v ₂ , up, double; T ₃ , neg.	R-T _{1,2} , sl. dep.; R-T _{1,2,4} , sl. elev.; T _{1,2,3,4,6} , diph.		R-T elev. all leads except lead III; T _{1,2,3,4,6} , up and peaked; T _{1,2} , diph.				5 mo.: R-T _{1,2,3,4,6} , iso.; R-T _{1,2,3,4,6} , elev. (high volt.); all T's up except T ₃ ; L.A.D.; semi- horizontal heart; ECG within normal limits	Pericarditis (second week): Suggestion of R.V. damage (R-T and T changes in v ₁ ; R-T changes v ₂); nonspecific damage indicated by R-T depression in early tracings
22. E. A., 44-1421; 46 yr. C, M	? Lower sternum just left midline; stab	7 hours: R-T, iso., except R-T _{v3} elev.; T's, up except v ₆ , low up	R-T _{1,2,3,4,6} , elev.; T's up except T ₃		R-T's iso.; T _{1,2,3,4,6} , neg.						Pericarditis; no definite myocardial damage
23. M. O., 43-14165; 29 yr. C, F	? Wound left sec- ond inter- space, 7.5 cm. from mid- sternal line; stab		R-T _{1,2,3} , elev.; T's, up; low volt.; L.A.D.	R-T's, iso.; T _{1,2,3} , low, dome.; low volt.; normal axis						11 mo.: ECG within normal limits (borderline volt)	Pericarditis only

TABLE V. LATE ELECTROCARDIOGRAPHIC FINDINGS AMONG TWELVE PATIENTS WITH CARDIAC WOUNDS

CASE	NUMBER OF LEADS	TYPE OF FINDING	TIME OF FOLLOW-UP (MONTHS)	NUMBER OF PATIENTS
<i>A. Left Ventricular Wounds (Six Cases)</i>				
13, 12 (Fig. 2)	12, 9	Normal electrocardiogram	11, 30	2
8 (Fig. 6)	12	Inverted T_1, T_2, T_{V3-6} ; P-R = 0.24 sec.	8	1
14 (Fig. 6)	12	Diphasic $T_{1,2,V3,6}$; T_{V4} low up	21	1
10 (Fig. 6)	12	Diphasic $T_1 + T_{V2}$; inverted $T_2 + T_{V6}$	28	1
*6 (Fig. 5)	12	Inverted $T_{V2} + T_{V6}$; diphasic $T_2 + T_{V4}$; isoelectric T_1 ; low voltage; diminished R_{V4}	36	1
13	12	Low voltage of $T_1, T_2, + T_{V6}$	3½	—
<i>B. Right Ventricular Wounds (Three Cases)</i>				
3, 4 (Fig. 4)	6, 12	Normal electrocardiogram	3, 33	2
1 (Fig. 3)	12	Defective intraventricular conduction (incomplete right bundle branch block), right ventricular premature systoles; diphasic T_{V3}, T_{V5} ; inverted T_{V4} ($S_{V4} > R_{V4}$), left ventricular preponderance	35	1
<i>C. Pulmonary Vein and Pericardium (One Case)</i>				
17 (Fig. 1)	4	Elevated S- $T_{1,2,3}$ (recurrent pericarditis)	3	1
<i>D. Unknown Location (Two Cases)</i>				
21 (Fig. 7), 23	12, 12	Normal electrocardiogram	5, 11	2
<i>E. Total Cases (Twelve)</i>				
		Normal electrocardiogram	15.5 (Av.)	6
		Abnormal electrocardiogram	21.9 (Av.)	6

$S_{V4} > R_{V4}$ = S wave in V_4 exceeds R wave in V_4 in amplitude.

*Probable complicating anterior infarction.

auricular fibrillation (two cases), prolonged Q-T interval (one case), defective intraventricular conduction (one case), and prolonged auriculoventricular conduction (one case).

Pericarditis.—The evolution of the electrocardiographic effects of pericarditis is best considered in chronologic order since it follows a fairly regular course and since it is important to know what to expect at a particular stage.

RS-T Segment Patterns: Of the two tracings taken preoperatively (Cases 11, 15—Fig. 5), the first is within normal limits and the second shows the pattern of acute anterior myocardial infarction in which it is impossible to distinguish with certainty changes which may be due to the associated hemopericardium. There are eight patients with electrocardiograms taken preoperatively and/or during the first twenty-four hours. In the first patient, just mentioned (Case 11), with an essentially normal preoperative tracing, an electrocardiogram taken eight hours after the operation shows the characteristic changes of pericarditis. The findings in the second (Case 15) have been described. In a third patient (Case 17—Fig. 1), a tracing taken immediately postoperatively showed nonspecific abnormalities but twenty-two hours later is suggestive of acute pericarditis. Of the remaining five patients, two show definite pericarditis (Cases 9, 18—Fig. 1), one suggestive changes (Case 6), and two only nonspecific abnormalities (Cases 21, 22). Thus, in five of these eight patients, the electrocardiogram taken during the first day shows pericarditis as early as eight hours postoperatively.

By the second day and thereafter during the first two or three weeks, the characteristic upwardly concave elevations of the RS-T segments were almost uniformly present. Of the standard leads they involved Leads I and II most frequently and were present in Lead III also in only one patient. In three patients this segment was slightly depressed in Lead III. In the fourteen patients in whom there are sufficient tracings at this stage for analysis of changes of the RS-T segment, elevations disappear in from eight to eighteen days, averaging thirteen days (Figs. 1 and 2). Such elevation appears first in one or more of the precordial leads in three of the five cases suitable for determining this point. Ten patients have electrocardiograms with one or more precordial leads taken at the same time or within a few days of the time when this segment became isoelectric in the standard leads. In seven, the RS-T elevation in the precordial leads disappears simultaneously, while in the other three it persists for a longer time in the precordial leads. It is more striking in the precordial leads in eight of eleven cases suitable for comparison. In general, however, since the RS-T changes are easily visible in the standard leads in the great majority of cases, the precordial leads are only occasionally of additional help as far as this feature is concerned. In two patients RS-T elevation recurred. In one, this accompanied definite clinical signs of pericarditis. In the other, no pericardial findings were elicited, but the patient suffered from thoracic empyema which necessitated surgical drainage (Case 17—Fig. 1).

T-Wave Patterns: Abnormalities of the T waves during the days and weeks following a penetrating cardiac wound may be due to pericarditis, to the wound itself, or to nonspecific types of myocardial damage from shock, anemia, or other less frequent causes. The presence of these multiple factors might appear to make it impossible to ascribe a particular T-wave abnormality specifically to pericarditis. Nevertheless, from a consideration of the behavior of the T waves in uncomplicated pericarditis of other types, it is possible to distinguish certain trends of influence upon the T waves of the pericardial factor in the present series of patients. In various types of pericarditis and in the present patients the

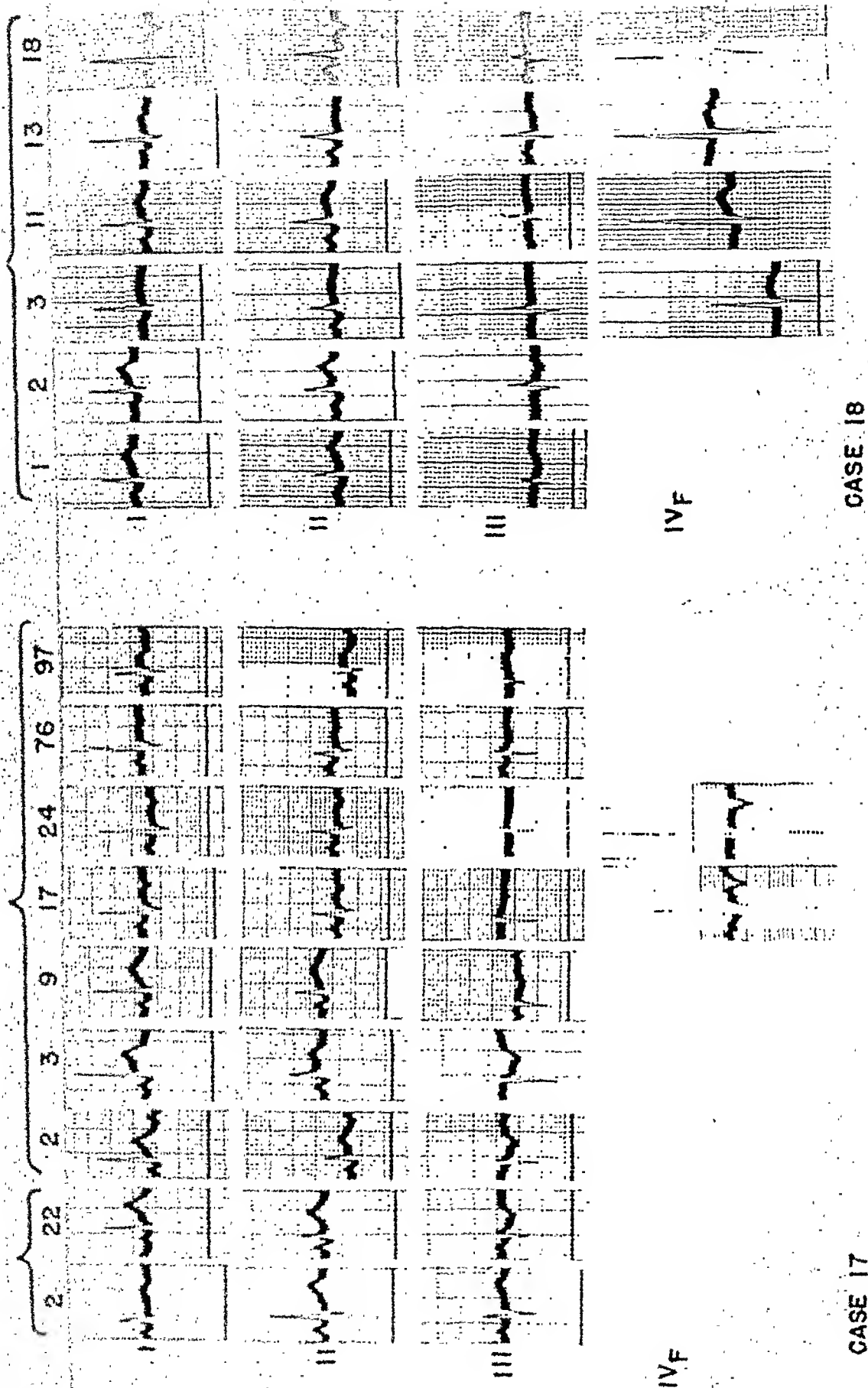


Fig. 1. - Electrocardiograms in two cases without ventricular wounds illustrating characteristic patterns of pericarditis.

Case 17. Stab wound of pericardium and pulmonary vein; myocardium intact. Emphysema drained at three months. Note (a) appearance of effects of pericarditis at twenty-two hours; (b) return of R-T segment to isoelectric level and appearance of inverted T waves at seventeen days; (c) persistence of T-wave inversion at seventy-six days; (d) recurrence of R-T elevations at ninety-seven days (recurrent acute pericarditis).

Case 18. Stab wound, left atrium. Note (a) early R-T elevation on first day; (b) classical pericarditis on second day; (c) slight notching of $P_1 + P_2$ suggesting left atrial damage; (d) return of R-T to isoelectric with diphasic $T_1, 2, 3$ on thirteenth day; (e) cove-plane T-wave inversions on eighteenth day. Note resemblance to each other and to corresponding days in tracings in Fig. 2. Illustrating cases with ventricular wounds.

T waves are frequently tall and peaked during the first part of the early period when RS-T elevation is present. These peaks tend to round off within a few days, but inversion nearly always occurs later, after the RS-T elevation has disappeared at the end of the second week or the early part of the third week

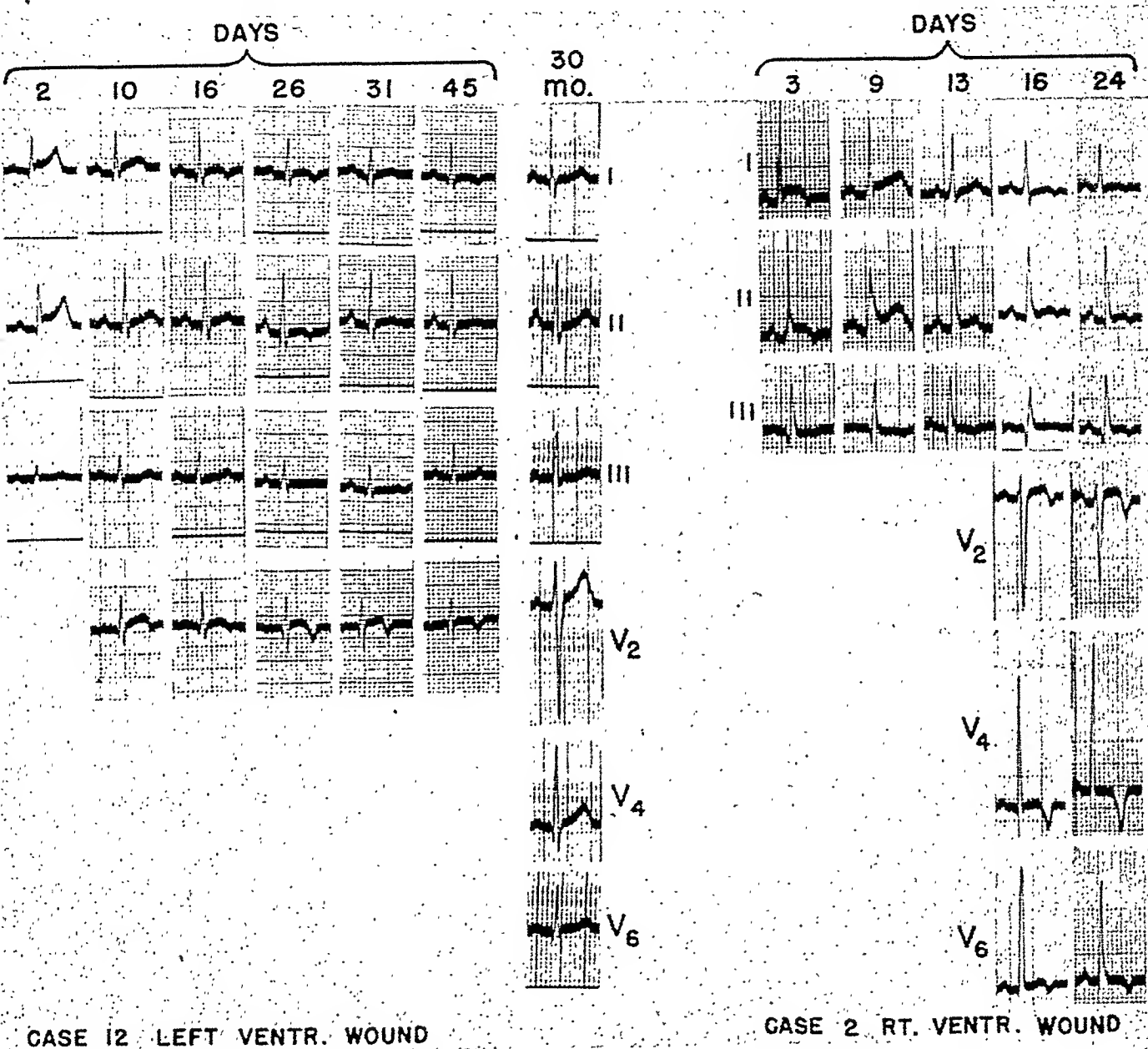


Fig. 2.—Electrocardiograms in right and left ventricular wounds illustrating preponderant influence of pericarditis.

Case 12. Stab wound of left ventricle. Note (a) recurrent acute pericarditis at thirty-one days with reversal of T-wave direction in standard leads; (b) so-called "late T₁ pattern" at forty-five days; (c) normal electrocardiogram at thirty months.

Case 2. Stab wound of right ventricle. Note (a) diphasic T_{1,2} at three days, suggesting non-specific myocardial damage; (b) lack of localizing pattern, with inversion of T waves in all leads, characteristic of pericarditis, at twenty-four days.

(see Figs. 1 and 2). In the present series the tracings of only six of twenty-one patients with electrocardiograms taken during the first week show diphasic or inverted T waves in leads other than III or V₁, whereas these changes are present in twelve of thirteen patients with tracings taken during the third week. Among

ten patients with frequent electrocardiograms, inversions of T waves appear between the eleventh and nineteenth days, averaging sixteen days. Their presence during the first week is associated with clinical or other electrocardiographic evidences of myocardial damage (Cases 1, 2, 5, 8, 14, and 19).

A second consideration relating the abnormalities of the T waves to pericarditis is the tendency in various types of generalized pericarditis toward widespread, more or less persistent inversions of T waves. Of the present cases suitable for analysis of this point, diphasic or inverted T waves are present in each of the standard leads from the extremities in eight of fifteen cases and in each precordial lead in five of ten cases. Thus in many cases the wide distribution seems to exclude localized myocardial damage, and the persistence and depth of these inversions excludes nonspecific types of myocardial damage as the sole or most important causes.

A third consideration is the presence in two patients (Fig. 1), without wounds of the ventricles, of abnormalities of the T waves closely similar in the time of their appearance, contour, and distribution to those seen in patients with wounds of either ventricle (Fig. 2). Since the wounds did not involve the ventricles, they cannot explain directly the abnormalities of the T waves. Nonspecific ventricular myocardial damage incident to shock, anemia, or displacement of the heart would not be as persistent. Exactly comparable changes are present in many cases of uncomplicated pericarditis of varied etiology. Therefore, pericarditis is the chief cause of these abnormalities in these two patients. The similarity of the pattern to that seen in wounds of either ventricle (compare Figs. 1 and 2) indicates the importance of pericarditis as a factor in the production of the electrocardiographic findings in ventricular wounds.

Low voltage of the QRS complexes of the standard leads from the extremities is present in six patients. This change is consistent with, though not pathognomonic of, pericarditis.

Localizing Findings. -

Right Ventricular Wounds: Five patients (Cases 1 to 5) were found at operation to have wounds of the right ventricle. The electrocardiograms of two patients show definite evidences of localized right ventricular myocardial damage as illustrated in Fig. 3 and described in the legend. One factor complicating the interpretation in Case 5 is the presence at autopsy of chronic rheumatic heart disease with mitral stenosis and insufficiency and right ventricular hypertrophy. However, the heart weighed only 410 grams and there was a small hemorrhagic extravasation in the interventricular septum which, along with the wounds of the right ventricle, seems to be a better explanation of the right bundle branch block. Furthermore, right ventricular hypertrophy would not explain the R-T segment elevations which are most marked in the precordial leads over the right ventricle. In one patient (Case 1) there was coincidental asymptomatic hypertensive cardiovascular disease with moderate left ventricular hypertrophy and probably also syphilitic aortitis. However, localized myocardial damage as indicated by the T-wave changes in Lead V_2 - V_3 which are not present in Lead V_4

would be very unusual in either of these two conditions. Also, the equal amplitude of the R and S waves in Lead V_4 indicate that the precordial electrode was near the interventricular septum. This corresponds with the location of the wound in the right ventricle near the septum.

Two additional patients in this group have questionable localizing findings. Pertinent tracings are shown in Fig. 4. Case 3 with a " T_2, T_3 pattern" is considered questionable because of the fact that pericarditis may cause inversions of T waves at this time and in these leads alone (vide infra). However, the number of reported cases of right ventricular wounds with persistence of this pattern beyond a three-month period indicates that this may be valid as a localizing

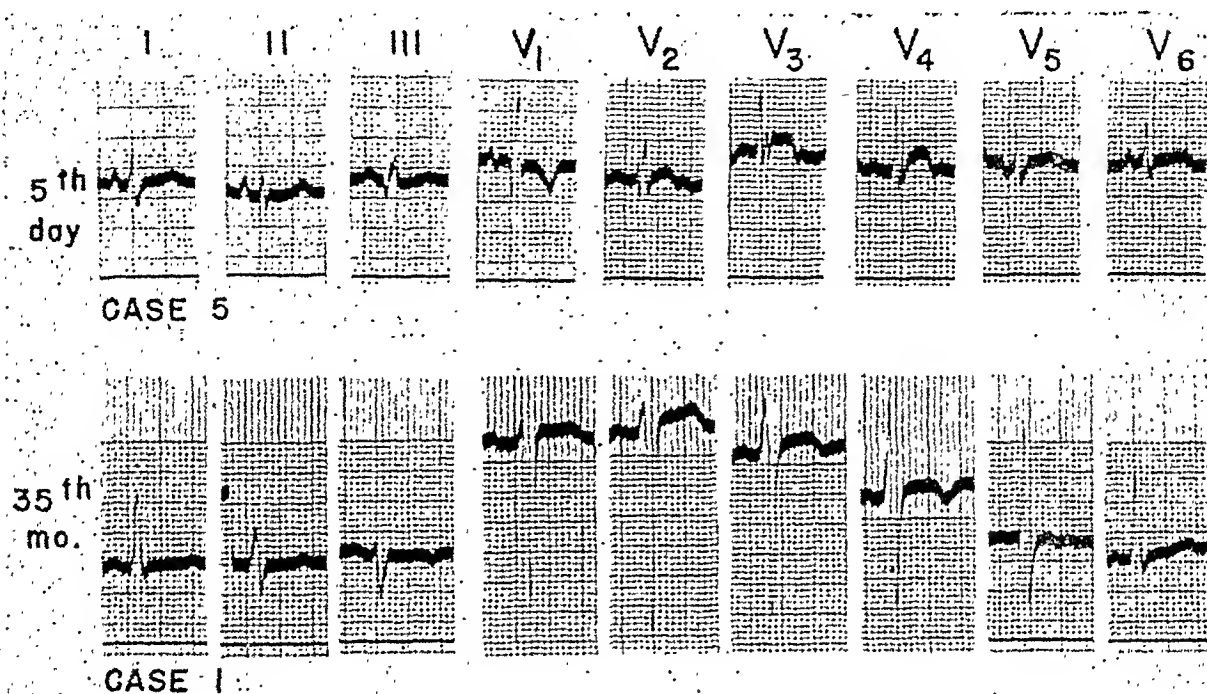


Fig. 3.—Definite localizing patterns in right ventricular wounds.

Case 5. Incomplete right bundle branch block; elevation $R-T_{V_3, 4}$, indicating localized subepicardial process.

Case 1. Note (a) late localized T-wave changes in V_3-V_5 corresponding to location of wound at left border of right ventricle; (b) incomplete right bundle branch block; (c) left ventricular preponderance due to associated hypertensive cardiovascular disease.

pattern in some instances. The evidence of localized damage in Case 4 is admittedly slender, and the observed elevations of the R-T segments in Lead V_2 on the fifteenth day could be dependent upon the high voltage of the QRS complex. However, they do suggest a localized subepicardial process. In the final patient (Case 2—Fig. 2), the electrocardiographic abnormalities are attributable to pericarditis.

Left Ventricular Wounds: There are eleven patients in whom left ventricular wounds were discovered at operation. In six definite electrocardiographic findings of left ventricular damage thought to be due to the wound are present. Electrocardiograms in two of these patients with known or probable injury to the left coronary artery are shown in Fig. 5. It is possible that in the second (Case 6) the diminished R waves are due to the wound itself. However, if this

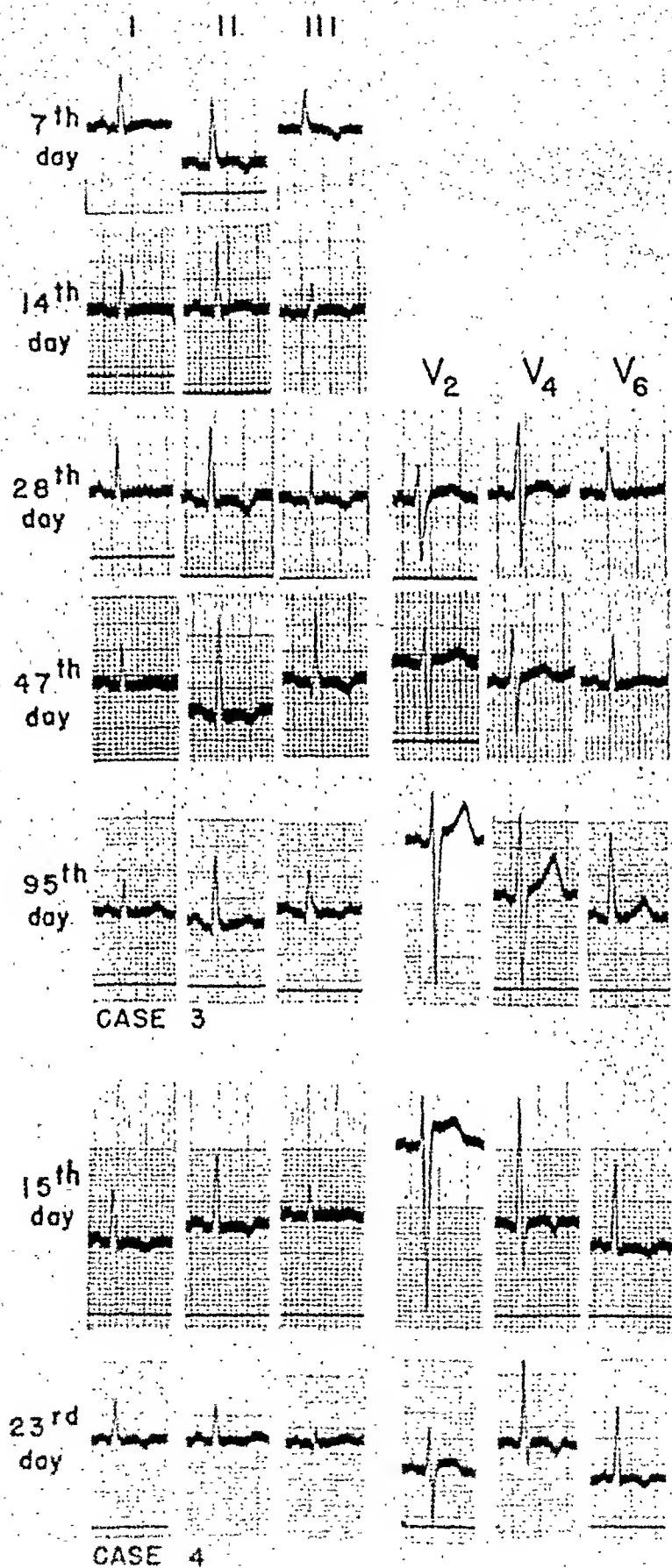


Fig. 4. —For legend, see opposite page.

were so, one would expect Q patterns or their equivalents in more of the cases with multiple precordial leads. The infrequency of this finding as well as the fact that the wound was very close to the left coronary artery makes it probable that this vessel was occluded, resulting in an anteroapical myocardial infarct. In both of these cases the pattern of anterior infarction gives indirect evidence of the location of the wound in the region of the left coronary artery.

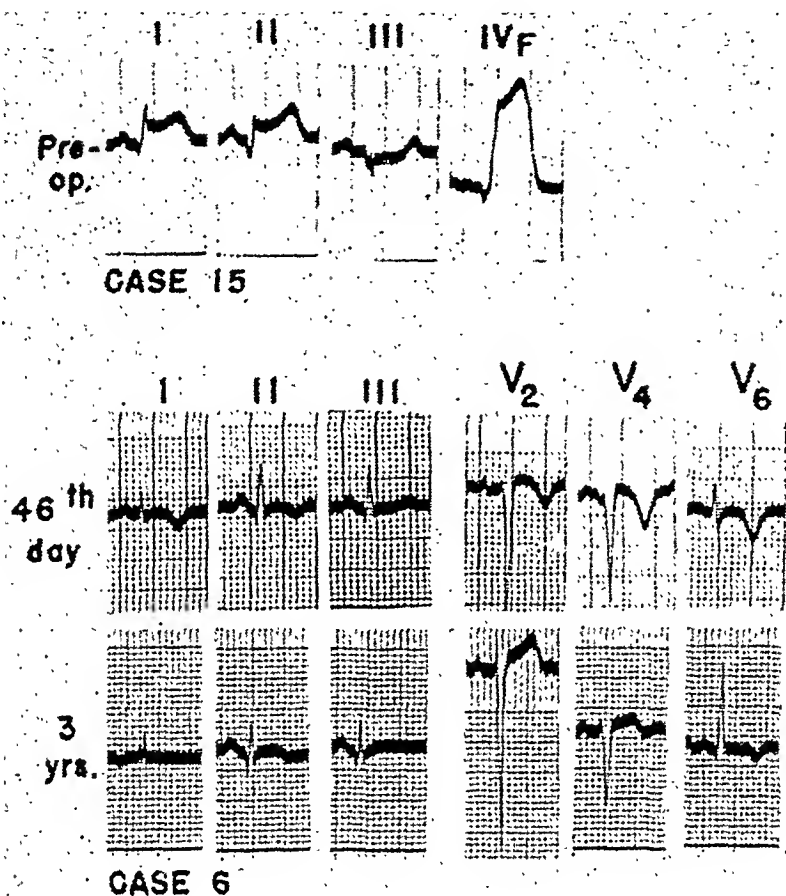


Fig. 5.—Left ventricular wounds with known or probable injury to left coronary artery.

Case 15. Patient found to have laceration of left ventricle dividing descending branch of left coronary artery. Note Q pattern, marked R-T elevation characteristic of recent anterior infarct. Unusual degree of elevation probably partly due to hemopericardium.

Case 6. Wound 3 to 4 mm. from left coronary artery; attempt made to avoid its suture. Note (a) very small R waves in V₄ probably due to anterior infarction, possibly to wound itself; (b) regression of T-wave inversions, persistently small R waves at three years.

Four of the six patients with left ventricular wounds with definite localizing findings have T-wave changes in Leads I and II and in the precordial leads over the left ventricle. Fig. 6 illustrates three such cases. Each of these young men was re-examined completely by me at the time of the last recorded electrocardiogram, and hypertension, valvular lesions, and left ventricular enlargement were excluded. Furthermore, the precordial leads do not show left ventricular hyper-

Fig. 4.—Right ventricular wounds with questionable localizing signs.

Case 3. Note preponderant inversion of T_{2,3} persisting through the forty-seventh day, the so-called "T₂, T₃ pattern."

Case 4. Note (a) isolated elevation of R-T segment in V₂ on fifteenth and twenty-third day, suggesting localized subepicardial process in right ventricle; (b) presence of so-called "late T₁" pattern on twenty-third day, here associated with a right instead of a left ventricular wound and probably due to subacute stage of pericarditis.

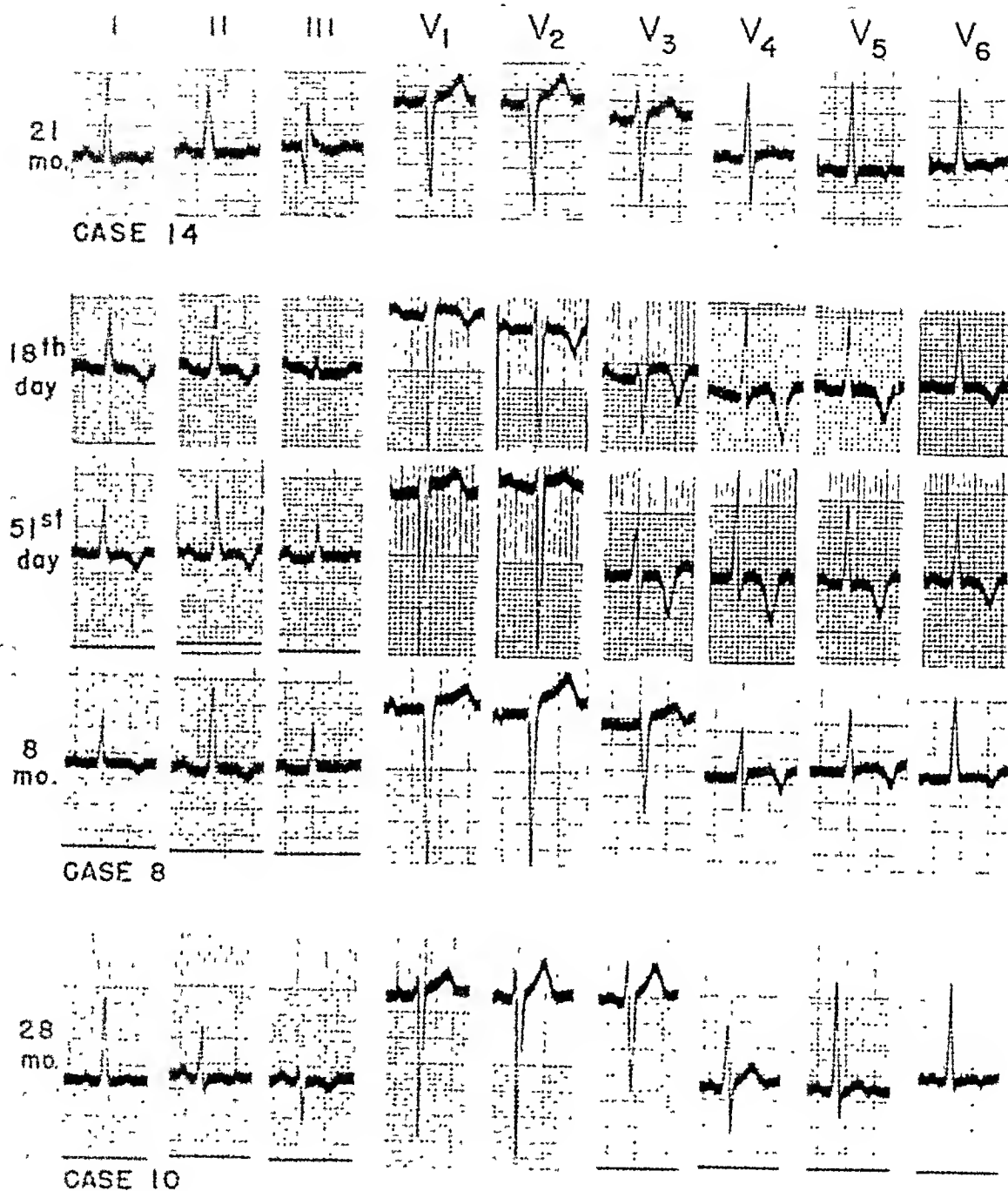


FIG. 6. Left ventricular wounds with localizing T-wave patterns.

CASE 14. Inverted T waves in Leads I, II, $V_3 + V_4$, Q_3 postural (see Table IV). [Inverted T waves previously present in V_2 and V_4 at fifty-one days and in V_4 at ninety-three days (not shown) have disappeared, probably indicating decrease in size of damaged area, localization in anterolateral left ventricle.] Cardiovascular examination otherwise negative at twenty-one months.

CASE 8. Note (a) deep T waves in V_3-V_4 on eighteenth day, the depth and contour suggesting myocardial damage rather than pericarditis alone; (b) decreased height of R wave in V_2 on eighteenth day, suggesting involvement of almost entire thickness of ventricular wall at this point; (c) persistent prolonged A-V conduction. Cardiovascular examination normal at eight months except wide splitting of first cardiac sound.

CASE 10. Persistent lateral left ventricular damage at twenty-eight months in absence of symptoms and physical or roentgen abnormalities.

trophy, since the time intervals from the initial QRS deflections to the peak of the R waves are 0.04 second or less in the leads over the left ventricle. For these reasons it may be assumed safely that coincidental cardiac disease is not a factor. Inspection of Table IV reveals that T-wave inversions in Cases 10 and 14 were present also in a number of earlier tracings during the first and second months. The difficulty in interpreting these earlier T-wave changes as due to localized left ventricular injury is shown by the fact that each of the three patients with right ventricular wounds (including Case 2—Fig. 2, and Case 4—Fig. 4) with tracings during this intermediate period showed abnormalities in the same leads.

When the T waves are as deep at any time as those in Case 8 of Fig. 6, localized damage may be assumed to be present since pericarditis alone rarely produces such T waves. The T-wave inversions occurring during the first week may indicate localized ventricular injury since pericarditis rarely causes inversions at this time, particularly if elevation of the R-T segment is present concurrently. However, nonspecific types of myocardial damage incident to shock, anemia, or the operative procedure may produce similar changes during this period, and so, again, it is unsafe to consider them as localizing findings.

The same considerations regarding the persistence of effects of pericarditis apply to the significance of the disappearance of abnormalities of the T waves in certain precordial leads while they are still present in others (see Case 6—Fig. 5). This may be due to the subsidence of the generalized pericarditis and perhaps should be so considered in most cases with tracings during the first two or three months. However, it is probable that in some of these tracings this represents a diminution in the size of the injured area. When it is large, it may affect the T waves in leads taken over the opposite ventricle, as is commonly seen in leads over the right ventricle in instances of anteroseptal infarcts of the left ventricle due to coronary heart disease.

Case 12 (Fig. 2) is considered to show questionable localizing findings since the last abnormal electrocardiogram showing limitation of T-wave abnormalities to Leads I and IVF is taken at forty-five days, during a period when pericarditis could still be exerting its effects. Of the four patients without localizing changes, two (Cases 9 and 16) had only one or a few electrocardiograms, and these were taken during the first week, and the other two (Cases 7 and 11) had tracings only during the first month. All showed typical changes of pericarditis.

Wounds Not Involving the Ventricles: The electrocardiograms of the two patients with wounds not involving the ventricles are shown in Fig. 1. In a patient with a left auricular wound (Case 18), the only localizing finding is notching of the P waves in Leads I and II. This is considered to be of questionable localizing significance because it is not marked enough to be definitely abnormal.

Wounds in Patients Without Operation: Two of the five patients have electrocardiograms with definite localizing findings (Cases 19 and 20—Fig. 7). Both T and Q patterns are present. The presence of Q waves raises the question of whether the coronary arteries were involved in the lacerations. In Case 19 the existence of a cardiac wound was not suspected until the electrocardiogram

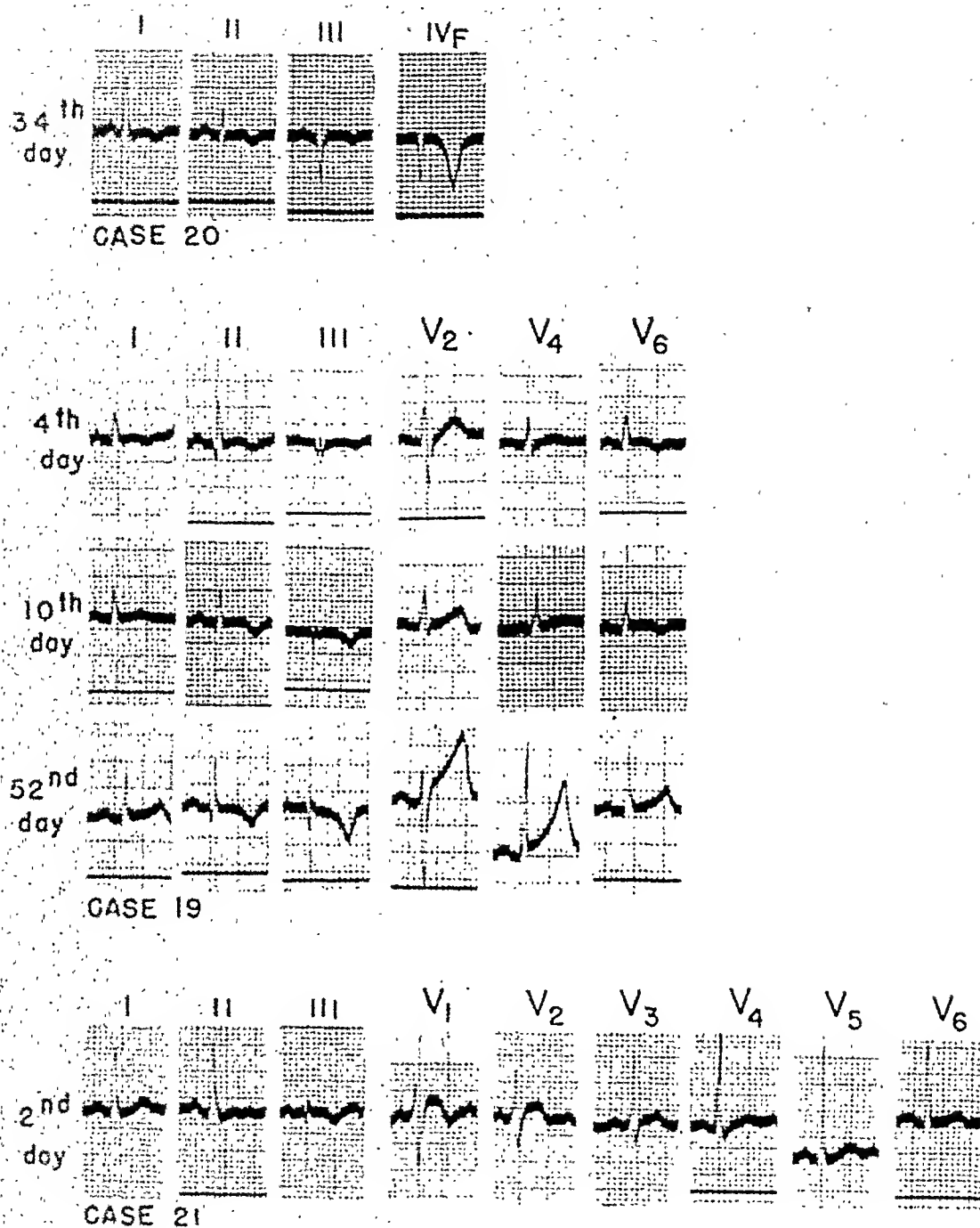


FIG. 7.—Electrocardiograms in cases without operation.

Case 20. Q wave and deeply inverted T wave in Lead IV F indicative either of a laceration of the descending branch of left coronary artery with resultant anterior myocardial infarction or a ventricular wound involving complete thickness of myocardium.

Case 19. Note (a) Q, Q_s and T_s, T₃ pattern, tall T waves in precordial leads at fifty-two days, indicative localized damage to posterior basal aspect of left ventricle either as direct result of wound or through infarct caused by laceration of right coronary artery. (Patient was stabbed in the back with a long knife.)

Case 21. Isolated elevation of R-Ty₃₊₂ suggests subepicardial myocardial process localized over right ventricle.

was obtained. This patient, a Negro 26 years of age, was stabbed in the back with a long knife in two places, both between the levels of the second and fifth dorsal vertebrae, with resulting left-sided hemopneumothorax. The initial period of shock was short, the degree of anemia only moderate, and the Kline test of the blood serum for syphilis negative. There were no symptoms or findings of cardiac failure. Cardiac examination revealed a pericardial rub on the second day and a roentgenogram showed slight cardiac enlargement. At first there was displacement of the mediastinum to the right, but this and the pleural effusion had practically disappeared by the eighteenth day. The well-marked Q and T patterns in Leads II and III may have been due merely to the wound of the posterior basal portion of the left ventricle, but in spite of the uneventful clinical course it is suspected that the right coronary artery was lacerated with the resulting electrocardiographic findings which are classical for an infarct in this area.

The other patient (Case 20), a Negro 27 years of age, presented an oblique laceration two inches long in the third left intercostal space near the mid-clavicular line, with resulting left hemopneumothorax. The postoperative course was stormy with tachycardia and dyspnea. The same considerations apply to the question of laceration of a coronary artery in this case as in the one just discussed.

A third case (Case 21—Fig. 7) shows elevation of the R-T segments in Leads V_1 and V_2 only, which is regarded as suggestive evidence of early subepicardial myocardial damage over the right ventricle. There are no localizing findings in the remaining two cases.

FOLLOW-UP STUDIES.—The purpose of this part of the study was threefold: first, to obtain electrocardiograms at a late enough date to avoid the complicating patterns of pericarditis; second, to attempt to correlate the electrocardiographic findings with other evidence bearing upon the cardiac status of these patients; and third, to look for evidences of constrictive pericarditis. The first aspect of this study has been incorporated into the preceding discussion, but these late electrocardiographic findings are listed in Table V for comparison with Tables II and III.

The symptoms and physical, roentgenologic, and electrocardiographic findings in eight patients examined by me at periods varying between five and thirty-six months following a cardiac wound are shown in Table VI. It is notable that in the first three cases with normal electrocardiograms all other objective findings are likewise entirely normal. However, all of these patients have symptoms. None of these are clearly of cardiac origin, and in each case there are unmistakable evidences of neurosis. The remaining five patients have abnormal electrocardiograms. In three of these other definite objective evidences of cardiac damage are present. In two the only other objective abnormality is the fluoroscopic finding of apical pleuropericardial adhesions not extensive enough to be clinically significant. Thus in the cases of these two patients the electrocardiographic findings are the only definite evidence of residual cardiac damage. In Case 1 the physical and roentgen findings are probably

TABLE VI. FINDINGS IN FOLLOW-UP STUDIES OF EIGHT PATIENTS

CASE	TIME OF FOLLOW-UP (MONTHS)	SYMPTOMS	CARDIAC FINDINGS	VENOUS PRESSURE (CM. H ₂ O)	ROENTGEN FINDINGS	ECG
13	11	Precordial heaviness; slight dyspnea; questionable orthopnea; numbness and "weakness" of left side of chest since blow to operative site sustained at factory	Normal size; no murmurs; B.P., 120/88; no pulsus paradoxus; no precordial retraction	6 7	Normal-sized heart on 7-foot plate taken at 3½ months	Normal
21	5	Nervousness; slight dyspnea; slight palpitation	Normal size and sounds; no murmurs; B.P., 124/88; no precordial retraction	--	Normal-sized heart on previous 7-foot film.	Normal
23	11	Nervousness; poor general health, precordial sticking pain, progressive dyspnea (patient's husband in prison; she requires welfare assistance)	Normal size and sounds; no murmurs; B.P., 108/78; no evidence of cardiac failure; no precordial retraction	9 0	Heart normal in size and contour on 7-foot film	Normal
1	35	None; returned to work two weeks after discharge from hospital; can easily run a block	Moderate enlargement; tambour aortic second sound; no murmurs; B.P., 194/116; no precordial retraction; grade 11+ hypertensive retinopathy	10 8	Moderate enlargement of hypertensive type; slight diffuse aortic dilatation; cardiac pulsations not forceful but no localized bulging during systole	Right ventricular myocardial damage; left ventricular hypertrophy

6	36	Has not worked since, "afraid to strain my heart"; questionable dyspnea; precordial aching	Apical impulse within midclavicular line; occasional premature systoles; no murmurs; normal sounds; B.P., 130/96; heart shifts with change of position; no pulsus paradoxus	7.0	Minimal lag in contraction at apex; slight left ventricular enlargement	Left ventricular damage; probable old anterior infarct
8	8	Slight palpitation; substernal tightness; good exercise tolerance	Normal size; wide splitting of first cardiac sounds; very soft apical systolic murmur; B.P., 124/90	5.0	Heart normal in size and contour on 7-foot film	Left ventricular myocardial damage; prolonged A-V conduction
10	28	None; slight palpitation noticed for one year has disappeared	Skin retracts with systole in small area near sternum; normal size and sounds; no murmurs or pulsus paradoxus; B.P., 128/80	7.0	Pulsations of good quality; visible apical adhesion; normal size and contour on 7-foot film	Left ventricular damage
14	21	Has limited his activities but no symptoms during ordinary activities	Normal size; no murmurs; aortic second sound slightly accentuated; cardiac sounds somewhat distant; systolic precordial retraction; no pulsus paradoxus or Broadbent's sign; B.P., 134/90	7.0	Normal size and contour; no bulging during systole; apical pericardial scar	Left ventricular damage

due chiefly to the associated hypertensive heart disease, whereas the electrocardiogram shows the effect of this complication and also of the right ventricular damage caused by the wound. While two of these five patients presented symptoms which were hard to evaluate, both exhibited abnormal objective findings in addition to the electrocardiogram. Evidences of chronic adhesive pericarditis sufficient to cause systolic retraction of ribs, fixation of the heart, or pulsus paradoxus were not observed, and the venous pressure in the antecubital vein was found to be normal in the seven patients tested.

COMMENT

REVIEW AND DISCUSSION OF THE ELECTROCARDIOGRAPHIC FINDINGS AT VARIOUS STAGES.—

*Early Stage (Preoperative and First Twenty-four Hours).—*The findings among the thirty-one cases depicted in the literature are described in detail in the foregoing and are summarized in Table I. The findings among eight cases in the present series are presented in the description of the RS-T segment patterns of pericarditis, in Table IV, and are illustrated in Figs. 1 and 5. Combining the two series, there were nine patients with preoperative tracings. Three showed definite evidence of an anterior myocardial infarct; one, right bundle branch block; one, definite pericarditis; two, suggestive pericarditis; and one, nonspecific changes: one was normal. The findings in these cases have the most direct bearing upon the question of the value of the electrocardiogram in the preoperative diagnosis of cardiac involvement in a thoracic wound. They indicate that definite evidences of cardiac involvement may be found in a sizeable proportion of such cases but that occasionally normal or nonspecific patterns may occur. From the standpoint of operative criteria, the physical and fluoroscopic evidences of cardiac tamponade are more directly applicable.

In the combined total of thirty-nine patients with one or more tracings taken preoperatively and/or during the first twenty-four hours, the electrocardiograms were diagnostic of the presence of myocardial infarction, bundle branch block, or pericarditis in twenty-one instances and suggestive of one of these conditions in an additional nine instances. However, in spite of the fact that it is at this stage that shock, anemia, and displacements of the heart are most prominent and are added to the direct effects of the wound, there were five instances in which the electrocardiogram was essentially normal. In eight patients, including some with suggestions of other lesions, nonspecific abnormalities were present. In several instances when the first electrocardiogram was taken preoperatively or within a few minutes or hours following operation, subsequent tracings during the first twenty-four hours showed the appearance of evidences of pericarditis or infarction. Since shock, anemia, and displacements of the heart may occur in wounds of the thorax not involving the heart and may cause nonspecific electrocardiographic abnormalities including inversions of the T waves, these early electrocardiograms should be considered as indicating cardiac involvement only when patterns of infarction, bundle branch block, or acute pericarditis are present.

The first two of these patterns also provide information as to the site of the cardiac wound.

Early Intermediate Stage (Second Day Through the First Three Weeks).—

The description by Herve and Forero Sarabia of the series of events taking place during this period is given in the foregoing and adequately covers the characteristic RS-T and T wave patterns as seen in tracings depicted in the literature. The findings in the present series are very similar, and since they are predominantly those of pericarditis, they are described under that section. Reference to Table IV and to Figs. 1, 2, 4, and 7 will disclose the details as seen in individual cases in the present series. The general uniformity of the patterns is due to the practically universal presence of pericarditis which produces very characteristic changes at this stage. Thus, the patterns are usually similar regardless of the location of the wound. The exceptions are instances of right bundle branch block, as illustrated by Case 5 of Fig. 3, and also instances of laceration or ligation of a coronary artery with resultant myocardial infarction. However, during the first few days of the early intermediate period, the characteristic reciprocal depression of the RS-T segment in Lead III occurring with anterior infarction usually disappears due to the opposing effect of the pericarditis which tends to cause elevation in all leads. This same sequence of effects has been observed in experimental myocardial infarction² and in clinical instances of coronary heart disease with myocardial infarction complicated by pericarditis.¹ The second distinctive feature in the cases with complicating infarction is the presence of abnormal Q waves. They tend to remain for months or years and so may occur at any of the stages being considered. The rare occurrence of the Q₂-Q₃ pattern of the posterior infarction in a cardiac wound is shown in Case 19 of Fig. 7. Esophageal and unipolar leads from the extremities would have contributed valuable confirmatory evidence in this case. In anterior infarcts, the pathologic Q waves are best seen in the precordial leads. Case 15 (Fig. 5) is the only anatomically proved instance of myocardial infarction in the present series, although it is likely that Case 6 of Fig. 5, and Case 20 of Fig. 7 are additional instances of anterior infarction. The alternate explanation of these Q- or diminished R-wave patterns is that they are due to the effects of a wound which involves nearly all or the complete thickness of the ventricular wall in the region underlying the exploring electrode. As mentioned previously, if the wound itself caused the Q waves, they might be expected to appear more frequently, especially when multiple precordial leads are taken. In either event they represent a localizing effect of the wound. The absence of Q waves in the precordial leads in instances described in the literature in which ligation of the left coronary artery or its branches is known to have occurred is explained either by the infarct's not extending through the full thickness of the wall or being localized to an area not influencing the single precordial electrode employed. The idea that more adequate collateral circulation exists in hearts with previously normal coronary arteries and that therefore infarction may not occur has been proved to be false by the studies of Blumgart and co-workers.⁷³

In the first part of the early intermediate period, inversions of the T waves cannot be ascribed to pericarditis since it is known that they almost always

appear later in uncomplicated instances of this condition. Neither can they be considered as a direct effect of the cardiac wound since there is no discoverable relation between the leads in which they occur and the location of the wound. They are best considered as evidences of nonspecific myocardial damage and are probably often due to shock and anemia which are most marked at this stage. Occurrence of very deep T waves, such as those seen in the eighteenth day in Case 8 of Fig. 6, suggest myocardial damage rather than pericarditis because the latter is less often responsible for inversions of this depth.

Late Intermediate Stage (Three Weeks Through Three Months).—The point of greatest interest concerning the late intermediate stage is whether or not the effects of pericarditis disappear sufficiently so that patterns due to the cardiac wound itself can be recognized. As previously mentioned, the opinion has been expressed^{21,53} that this is possible after the second week. However, a review of the literature on the persistence of the effects of pericarditis of various other types does not support this opinion. Thus, Winternitz and Langendorf⁵⁸ stated that the T waves usually became inverted during the third week and that the inversion might last for several months, although this abnormality always disappeared later when healing had occurred. Holzmänn,⁷¹ in classifying the electrocardiographic changes during pericarditis, placed the "late acute phase" between the tenth day and the sixth week, the subacute stage between six weeks and two months. Perhaps the best idea of how long the electrocardiographic effects of the type of pericarditis accompanying cardiac wounds may persist is gained from a review of cases of atrial or pericardial wounds in which the persistent T-wave inversions are necessarily associated with the pericarditis, since these structures have no direct effect on the T waves. There are five cases^{6,15,53} (CASES 25-26,30¹) suitable for this purpose depicted in the literature. T-wave abnormalities are still present at forty-three, fifty-two, sixty, sixty, and ninety days. In two similar cases in the present series, abnormalities are present in the last electrocardiograms at twenty-four and ninety-seven days (Fig. 1).

There is some additional evidence for the persistence of the effects of pericarditis during this period. In Case 12 of Fig. 2 the reversal from negative to positive of the T wave in Lead I and the reappearance of elevation of the RS-T segment in Lead IVF in the tracing taken on the thirty-first day are characteristic of an acute flare-up of pericarditis. This makes it hazardous to consider the next tracing in this same case taken only fourteen days later which conforms to the so-called "late T₁ pattern" of left ventricular wounds as definitely due to the localized effect of the wound rather than to subacute pericarditis. The close similarity between the tracing at twenty-six days in this case to that of twenty-four days in Case 2 of Fig. 2 and that of twenty-three days in Case 4 of Fig. 4, both of the latter two occurring in wounds of the right ventricle, further illustrates the difficulties of ascribing localizing significance to changes in the T waves during this period. Case 3 of Fig. 4 illustrates the so-called "late T₂-T₃ pattern" of right ventricular wounds. While it is true that many types of right ventricular myocardial damage are reflected in these leads, it is also true that uncomplicated pericarditis may cause inversions of the T waves in these leads

alone.⁶⁹ Since it has been shown that pericarditis is frequently still active, it is doubted that such a pattern should be considered at this time as definitely due to the direct effect of the right ventricular wound.

Late Stage (Three Months or More After the Wound).—Excluding patients with complicating myocardial infarction, the three standard leads in approximately 50 per cent of patients with persistently abnormal tracings (Tables II and V) correspond very well with the previously described "late T₁ pattern" of left ventricular wounds and in most instances with the "late T₂-T₃ pattern" of right ventricular wounds. In the former the T wave in Lead I was always abnormal, whereas combined abnormalities of the T waves in Leads II and III did not occur. In the right ventricular wounds only one case showed T-wave abnormalities limited to Lead I, whereas the remaining cases showed either the T₂-T₃ pattern or right bundle branch block. This correspondence with the previously described T-wave patterns which were based upon electrocardiograms taken at periods from two weeks onward suggests that these patterns may appear earlier than three months. However, they are not as reliable then as later.

Among the cases depicted in the literature with a single precordial lead, there was only one patient in whom it was entirely normal. In two patients it constituted the chief although not the only abnormality. Its T wave was inverted in both right and left ventricular wounds as might be expected from its location, which usually overlies the vicinity of the interventricular septum and so exposes it to influences from either ventricle. For this reason and also because from experience in other diseases of the heart it is known that a single precordial lead may not record some right ventricular or lateral left ventricular lesions, multiple precordial leads would be expected to be superior in detecting small lesions and in indicating the location of the wound. This appears to be so as judged by the findings in these leads in the present series of patients. All of the patients with left ventricular wounds with persistently abnormal tracings showed abnormal T waves in Lead V₆, and all but one had abnormal T waves in Lead V₅, but there were three patients in whom this deflection was normal in Lead V₄. Since the location of this lead is the same as that usually chosen for a single precordial lead, the evidences of myocardial damage in these patients would have been missed by such a lead. While there was only one patient with a right ventricular wound in whom the tracings were abnormal at this stage, the T wave in Lead V₆ was upright and the maximum inversion occurred in Lead V₄, which corresponded to the location of the wound in the right ventricle near the septum.

Until these late tracings were obtained, there seemed to be some question as to whether the wound itself, in the absence of damage to a coronary artery or to the branches of the bundle of His, caused any detectable electrocardiographic changes. However, the later emergence of these patterns indicates that they were present earlier but usually indistinguishable from the changes due to pericarditis.

FOLLOW-UP STUDIES IN CARDIAC WOUNDS.—Apart from the electrocardiographic findings, no attempt has been made to review the literature concerning the

late results of penetrating cardiac wounds. As mentioned previously, there have been only thirteen cases with published electrocardiograms followed for more than six months. The most extensive study of late electrocardiographic and other clinical findings is that of Steffens,⁷⁴ although in it the electrocardiograms are not published. His 109 patients were German veterans of World War I who had sustained bullet wounds from ten to twenty years before re-examination. In only ten of the sixty-nine cases studied electrocardiographically with the standard leads from the extremities were the tracings abnormal. In several of these patients there was complicating disease of the heart sufficient to account for the abnormalities. In the remaining patients there were no other objective evidences of myocardial damage. Of the whole group, however, only 13 per cent had no complaints. For the most part, the symptoms were considered as psychogenic.

In the present study also the electrocardiograms exhibited the most constant and persistent objective abnormality. Because of this they are of value in indicating the need for some caution in the management of such cases, although the patient's symptoms and physical and roentgen findings must also be considered. In patients who have indefinite symptoms of a type suggesting a psychoneurosis, but whose physical and roentgen examinations disclose no abnormalities, the finding of a normal electrocardiogram, particularly when multiple precordial leads are taken, is strong evidence in favor of the functional origin of the complaints. It indicates the prime necessity of psychotherapy in their management.

SUMMARY AND CONCLUSIONS

1. A review of the literature on the electrocardiogram in penetrating wounds of the heart is presented including a tabular summary of thirty-one cases in which tracings were obtained during the first twenty-four hours and of an equal number in which they were taken three months or more (average, 7.1 months) after the wound.

2. The electrocardiographic findings in twenty-three similar cases observed at Detroit Receiving Hospital are described and illustrative examples presented. In sixteen of these cases, multiple precordial leads were obtained and in twelve the follow-up period was three months or longer (average, 18.5 months). Eight patients were completely re-examined by me at periods varying between five and thirty-six months (average, 19.1 months) following the wound, thus making possible a correlation of the symptoms and physical and roentgenologic findings with the electrocardiograms at this late stage.

3. In the present series of twenty-three patients, definite electrocardiographic evidences of pericarditis appeared in seventeen, in seven of whom no other abnormalities could be detected. Definite localizing patterns directly attributable to the wound were present in ten. In five of these the localizing findings appeared in early electrocardiograms and consisted of right bundle branch block (one case) or Q-wave patterns due either to complicating myo-

cardial infarction from injury of a coronary artery or possibly in some instances to involvement of the full thickness of the ventricular wall by the wound itself. In the other five cases the localizing patterns were not well-defined until three months or more after the wound. Four of these were instances of left ventricular wounds characterized by abnormalities of the T waves in Lead I and in one or more of the precordial Leads V_4 , V_5 , and V_6 . The one instance of a right ventricular wound in which a late tracing was obtained showed abnormalities of the T waves in Leads V_3 , V_4 , and V_5 , corresponding closely with the location of the wound in the right ventricle near the septum.

4. The clinical follow-up studies on eight patients in the present series indicates that the electrocardiogram exhibits the most persistent objective abnormalities. When present, they suggest the need for some caution in the management of the patient. When the electrocardiogram is normal in all leads, including those taken from multiple precordial stations, it is of aid in confirming the psychogenic origin of persistent subjective symptoms.

As judged by the findings in the present series and in those in which the electrocardiograms are depicted in the literature, the following conclusions are drawn:

1. Preoperative electrocardiograms show definite evidences of cardiac involvement in the majority of cases and therefore may aid in the decision as to whether or not the heart is included in a thoracic wound. Electrocardiographic findings such as those of pericarditis, bundle branch block, or myocardial infarction may be accepted as definite evidences of cardiac involvement, whereas T-wave abnormalities and minor deviations of the RS-T segments cannot be relied upon since they could be caused by shock, anemia, or displacements of the heart which are often present in thoracic wounds without cardiac involvement.

2. During the first twenty-four hours the incidence of abnormal tracings increases. Changes due to pericarditis frequently appear but usually at this time do not obscure the RS-T segment and T-wave patterns of myocardial infarction due to laceration or ligation of a coronary artery.

3. During the early intermediate period (second day through the first three weeks) the effects of pericarditis predominate and cause strikingly similar findings in the majority of the cases regardless of the location of the wound. The RS-T segment and T-wave changes of anterior myocardial infarction likewise may be obscured, although a sufficient number of precordial leads would be expected to show Q waves in most of such cases.

4. During the late intermediate period (three weeks through three months) the electrocardiographic effects of pericarditis may persist. This makes the T-wave patterns unreliable at this time for locating the site of the wound. In this period and in all of the previous periods localizing findings are provided chiefly by either bundle branch block or indirectly by Q-wave patterns of infarction.

5. The consistent finding of abnormalities of the T waves limited to one or more of the precordial Leads V_4 , V_5 , and V_6 in late tracings of patients with left ventricular wounds amplifies the previously described "T₁ pattern" and demon-

strates the superiority of such leads over a single precordial lead. The late tracing of one patient with a wound of the right ventricle, as well as clinical experience with multiple precordial leads in other right ventricular lesions, suggests that such leads may be expected to yield information not afforded by a single precordial lead and should amplify the previously described "T₂ pattern."

6. The failure to find differences in the electrocardiographic patterns resulting from wounds of different parts of the heart or between those with and without interruption of a sizeable coronary artery is usually due to the obscuring effects of pericarditis in most tracings except those taken either very early or after several months have elapsed. It may also be due to an insufficient number of leads or to not recognizing the distinctions between patterns of pericarditis and myocardial infarction.

7. Further investigation is needed to clarify two interesting questions raised by the findings in multiple precordial leads in the present study: (A) May the wound itself produce Q waves in one or more of these leads, or are these always due to an area of myocardial infarction from interruption of a coronary artery? (B) Is the progressive disappearance of inversion of the T waves in some of the precordial leads entirely due to the recession of generalized pericarditis, or may it be due partly to a decrease in the size of the wound and thus give valuable evidence of the healing process?

The author wishes to express his thanks to Dr. Morris H. Blau and other members of the Surgical Department for their help and cooperation in this study. Also he wishes to thank Dr. Gordon B. Myers for helpful advice and criticism.

REFERENCES

1. Barnes, A. R.: Electrocardiographic Pattern Observed Following Acute Coronary Occlusion Complicated by Pericarditis; Report of Cases, *AM. HEART J.* 9: 734, 1934.
2. Barnes, A. R., and Mann, F. C.: Electrocardiographic Changes Following Ligation of the Coronary Arteries of the Dog, *AM. HEART J.* 7: 477, 1932.
3. Bates, W., and Tally, J. E.: Electrocardiograms of Coronary Occlusion Following a Stab Wound in the Left Ventricle. *AM. HEART J.* 5: 232, 1929.
4. Benn, W. B.: Bullet Wound of the Heart, With Coronary Artery Ligation, *AM. HEART J.* 21: 375, 1941.
5. Benet, G., and Spivey, C. G.: Suture of Stab Wound of the Heart; Report of Case, *J. A. M. A.* 101: 1979, 1935.
6. Caviness, V. S., and Turner, H. G.: Puncture Wound of the Left Auricle With Tamponade and Recovery. *AM. HEART J.* 25: 693, 1943.
7. Cole, Warren H.: Suture of Wounds of Heart, With Report of Recent Case, *Ann. Surg.* 85: 647, 1927.
8. Davenport, G. L.: Suture of Wound of the Heart, *J. A. M. A.* 82: 1840, 1924.
9. Davenport, G. L., Blumenthal, B., and Cantril, S.: Electrocardiographic Studies of a Stab Wound of the Heart. *J. Thoracic Surg.* 5: 208, 1935.
10. Davenport, G. L., and Markle, P.: The Electrocardiogram in Stab Wounds of the Heart; Case Report, *J. Thoracic Surg.* 3: 374, 1934.
11. Eakin, W. W.: The Removal of a Large Needle From the Heart With Electrocardiographic Changes in Rhythm During Operation, *AM. HEART J.* 8: 540, 1933.
12. Fraser, W. A., and Texon, M.: Electrocardiographic Findings Associated With a Gunshot Wound of the Heart; Report of Case, *New England J. Med.* 225: 286, 1941.
13. Gillesby, W. J.: Cardiac Tamponade; Report of a Stab Wound in the Right Ventricle, *Mil. Surgeon* 95: 284, 1944.
14. Glavanis, W., and Schulenberg, B.: A Penetrating Stab Wound of the Heart; Operation; Recovery, *Lancet* 2: 132, 1937.

15. Glasser, S. T., Mersheimer, W. L., and Shiner, I.: Bullet Wound of Left Cardiac Auricle With Suture and Recovery; Review of Literature, *Am. J. Surg.* 53: 131, 1941.
16. Goldberger, H. A., and Clark, H. E.: Migration of Needle Into Heart Through Chest Wall: Surgical Removal: Electrocardiographic and Roentgenographic Studies, *J. A. M. A.* 105: 193, 1935.
17. Herfarth, H.: Beitrag zur Herzchirurgie (unter besonderer Berücksichtigung des Ekg), *Zentralbl. f. Chir.* 67: 2110, 1940.
18. Hyman, A. S., and Fisher, J. L.: Post-Traumatic Disturbances of the Heart, *AM. HEART J.* 2: 61, 1926.
19. Koucky, J. D., and Milles, G.: Stab Wounds of the Heart, *Arch. Int. Med.* 56: 281, 1935.
20. Linner, B.: Verletzungen des Herzens durch Nadeln, *Zentralbl. f. Chir.* 68: 208, 1941.
21. Merkel, H.: Durch Herznaht geheilte Stichverletzung des Herzens, *Zentralbl. f. Chir.* 66: 2323, 1939.
22. Mohr, H.: Spätfolgen einer Herznaht mit Unterbindung des Ramus descendens der Arteria coronaria sinistra, *Zentralbl. f. Chir.* 68: 11, 1941.
23. Mondry, F.: Das Elektrokardiogramm bei mehrfacher Herzstichverletzung, *Zentralbl. f. Chir.* 66: 743, 1939.
24. Nana, A.: Penetrierende operierte Herzwunde; Spätresultate, *Zentralbl. f. Chir.* 66: 2198, 1939.
25. Olin, C. B., and Hughes, J. D.: Stab Wound of the Heart With Coronary Ligation, *J. Thoracic Surg.* 9: 99, 1939.
26. Peitmann: Ueber Arbeitsfähigkeit nach Herznaht, *München. med. Wchnschr.* 86: 604, 1939.
27. Purks, W. K.: The Electrocardiographic Findings Following Ligation of Decending Branch of the Left Coronary Artery in Man, *AM. HEART J.* 7: 101, 1931.
28. Ramsdell, E. G.: Stab Wounds of the Heart, *Ann. Surg.* 99: 141, 1934.
29. Schlomka, G.: Elektrokardiographische Beobachtungen bei Herzstichverletzung, *Deutsche med. Wchnschr.* 57: 630, 1931.
30. Schwab, E. H., and Herrmann, G.: Alterations of the Electrocardiogram in Diseases of the Pericardium, *Arch. Int. Med.* 55: 917, 1935.
31. Solovay, J., Rice, G. D., and Solovay, H. V.: Electrocardiographic Changes in Stab and Gunshot Wounds of the Heart, With Review of Literature, *Ann. Int. Med.* 15: 465, 1941.
32. VanderVeer, J. B., and Norris, R. F.: The Electrocardiographic Changes in Acute Pericarditis; Clinical and Pathological Study, *AM. HEART J.* 14: 31, 1937.
33. Warthen, H. J.: Stab Wound of the Heart; Report of Case, *Ann. Surg.* 102: 147, 1935.
34. Weinstein, M.: Stab Wound of the Heart; Report of a Successful Operation, *J. A. M. A.* 122: 664, 1943.
35. Zerbini, E. de J.: Coronary Ligation in Wounds of the Heart, *J. Thoracic Surg.* 12: 642, 1943.
36. Abramson, P. D.: Stab Wound of the Heart, *New Orleans M & S. J.* 86: 376, 1933.
37. Angeli: Quoted by Solovay and others.³¹
38. Bruckner, J. D.: Stab Wound of the Heart; Case-Report of Successful Suture, *Ann. Surg.* 118: 46, 1943.
39. Clark, J. F.: Suture of Stab Wound of the Heart; Report of Case, *Texas State J. Med.* 29: 203, 1933.
40. Fischer, L.: Herzverletzung und Elecktrokardiogramm, *Arch. f. klin. Chir.* 188: 557, 1937.
41. Flaum, E.: Ueber die Bedeutung den Koronarveränderungen des Menschlichen Elektrokardiogramms, *Wein. Arch. f. inn. Med.* 23: 409, 1933.
42. Holubee: Quoted by Wood.⁶⁵
43. Junghans, H.: Zur Frage der Leistungsfähigkeit nach operativ behandelten Herzverletzungen, *Zentralbl. f. Chir.* 67: 2257, 1940.
44. Kienle: Quoted by Solovay and others.³¹
45. Kment: Quoted by Oppolzer.⁴⁸
46. Matti: Quoted by Solovay and others.³¹
47. Morris, K. A.: Penetrating Wounds of the Heart, *Am. J. Surg.* 41: 108, 1938.
48. Oppolzer, R.: Heilung eines Herzdurchschusses mit Durchtrennung des Hinteren absteigenden Astes der rechten Coronararterie nebst elektrokardiographischer Verfolgung, *Deutsche Ztschr. f. Chir.* 242: 620, 1934.
49. Rehn: Quoted by Oppolzer.⁴⁸
50. Scherf: Quoted by Oppolzer.⁴⁸
51. Schröder, C. H.: Naht einer zweifachen Stichverletzung des Herzens, *Zentralbl. f. Chir.* 67: 2345, 1940.
52. Williams, D. B.: Successful Suture of Stab Wound of the Heart, *New Orleans M. & S. J.* 95: 470, 1943.
53. Herve, L., and Forero Sarabia, A.: Estudio electrocardiografico de 30 heridas del corazon y del pericardio, *Medicina, Buenos Aires* 3: 387, 1943.

54. McGuire, J., and McGrath, E. J.: Penetrating and Lacerating Wounds of the Heart, *Tr. A. Am. Physicians* 56: 194, 1941.
55. Elkin, D. C., and Phillips, H. S.: Stab Wound of the Heart; Electrocardiographic Studies of Two Cases, *J. Thoracic Surg.* 1: 113, 1931.
56. Parade, G. W., and Rating, B.: Beitrage zum Problem der Herzverletzung, *Klin. Wchnschr.* 19: 1276, 1940.
57. Porter, W. B., and Bigger, I. A.: Nonfatal Stab Wounds of the Ventricle, With Electrocardiographic Signs of Coronary Thrombosis and Absence of Anginal Pain, *Am. J. M. Sc.* 184: 799, 1932.
58. Weinternitz, M., and Langendorf, R.: Das Elektrokardiogramm der Perikarditis, *Acta med. Scandinav.* 91: 141, 1938.
59. Blalock, A., and Ravitch, M. M.: A Consideration of the Non-Operative Treatment of Cardiac Tamponade Resulting From Wounds of the Heart, *Surgery* 14: 157, 1943.
60. Bland, E. F.: Foreign Bodies in and About the Heart, *AM. HEART J.* 27: 588, 1944.
61. Garretón Silva, A., Herve, L. L., and Fuenzalida, C. O.: Estudio electrocardiografico en dos intervenciones quirúrgicas por heridas del corazón, *Rev. med. de Chile* 70: 793, 1942.
62. Linder, H., and Hodo, H.: Stab Wounds of the Heart and Pericardium, *South. M. J.* 37: 261, 1944.
63. Nissen, R.: Advances in Heart Surgery, *J. Internat. Coll. Surgeons* 6: 99, 1943.
64. Stenbuck, J. B.: Two Cases of Successful Suture of Penetrating Stab Wounds of the Heart, With Some Observations on the Subject, *J. Mt. Sinai Hosp.* 7: 520, 1941.
65. Wood, P.: Electrocardiographic Changes of a T₂ Pattern in Pericardial Lesions and in Stab Wounds of the Heart, *Lancet* 2: 796, 1937.
66. Scott, R. W., Feil, H., and Katz, L. N.: The Electrocardiogram in Pericardial Effusion; Clinical, *AM. HEART J.* 5: 68, 1929.
67. Herrmann, G., and Schwab, E. H.: Some Experimental and Clinical Electrocardiographic Observations on R-S-T and T Changes in Pericarditis. *Tr. A. Am. Physicians* 49: 229, 1934.
68. Noth, P. H.: The Electrocardiogram in Pericarditis, Thesis, University of Minnesota, 1938.
69. Noth, P. H., and Barnes, A. R.: Electrocardiographic Changes Associated with Pericarditis, *Arch. Int. Med.* 65: 291, 1940.
70. Forero Sarabia, A.: Electrocardiografía en las heridas del corazón, Thesis, University of Chile, 1940.
71. Holzmänn, M.: Elektrokardiographische Befunde bei Perikarditis, *Helvet. med. acta* 3: 249, 1936.
72. Blau, M. H.: Wounds of the Heart, *Am. J. M. Sc.* 210: 252, 1945.
73. Blumgart, H. L., Schlesinger, M. J., and Zoll, P. M.: Angina Pectoris, Coronary Failure and Acute Myocardial Infarction, *J. A. M. A.* 116: 91, 1941.
74. Steffens, W.: Arbeit und Gesundheit. Heft 27. Herzsteckschüsse, Leipzig, 1936, Georg Thieme.

ADDENDUM

Since this article was submitted for publication, four of the five patients with persistently abnormal electrocardiograms listed in Table VI (Cases 6, 8, 10, and 14) were re-examined during August through October, 1946, approximately two years following the examination recorded in Table VI.

Their status as far as the presence or absence of symptoms is concerned remains unchanged except for the occurrence of mild dyspnea upon exertion in Case 8. Physical examination revealed no notable change in cardiac findings and no pulsus paradoxicus or venous distention in any case. Moderate hypertension appeared in Case 10. Roentgenograms were practically identical in all cases except Case 10, in which there was an increase in the transverse diameter of the heart of 0.5 centimeter. The slightness of the change and the presence of some rotation of the thorax negated the significance of this finding. The electrocardiogram in Case 6 showed disappearance of low voltage, a change in the T waves in Lead I from isoelectric to diphasic, those in Lead V₄ from diphasic to inverted and persistence of T-wave inversion in Leads V₂ and V₃. These changes in the T waves might have been due to a change in the position of the heart from an intermediate to a more vertical position. In Case 8 prolonged auriculoventricular conduction persisted, but the T waves in Leads V₄ and V₅ were slightly less deeply inverted. The T waves in Lead V₂ became diphasic from normally upright. In Case 10 there was no significant change in the electrocardio-

gram. In Case 14 the T waves in Leads I, II, and V_6 became low upright from diphasic and those in Leads V_4 and V_5 normally upright from low upright and diphasic, respectively.

In summary, during this two-year period there was little change in the history, physical, or roentgenographic findings in these four patients. The electrocardiogram of one patient remained unchanged, those of two showed minor changes, while that of the fourth patient revealed definite improvement in the status of the myocardium.

A CLINICAL EVALUATION OF POWDERED HUMAN BLOOD CELLS IN THE TREATMENT OF ULCERS OF THE EXTREMITIES ASSOCIATED WITH VASCULAR DISORDERS

MILTON W. ANDERSON, M.D.,* NELSON W. BARKER, M.D.,† AND
THOMAS H. SELDON, M.D.‡
ROCHESTER, MINN.

THE treatment of ulceration of an extremity which is affected by vascular disease is frequently a serious problem. The ischemic ulcer associated with occlusive arterial disease is notoriously indolent and resistant to local or topical applications. It may have been produced by major or minor trauma or local infection or it may persist after the sloughing of gangrenous tissue. It may occur at the site of amputation of a digit or portion of a limb. It is usually infected and its base is frequently choked with leucocytes. Because of ischemia the tissue at the base and margin of the ulcer is very sensitive to heat, cold, and chemical irritation. Detergents or other topical applications which have even the slightest tendency to cytotoxicity may affect such ulcers adversely. The use of ointments or wet dressings is often tolerated poorly. The ulcers are frequently painful. In spite of measures designed to produce vasodilatation and improve arterial blood flow, they may persist for weeks or months and cause prolonged suffering and disability.

The so-called stasis ulcer associated with chronic venous insufficiency which follows thrombophlebitis or complicates extensive primary varicose veins is somewhat less serious and may be easier to heal. However, it is often large, indolent, and infected, particularly when neglected. Many such ulcers will respond favorably to rest in bed with elevation of the limb and the application of almost any bland wet dressing. Stasis ulcers, also, are sensitive to strong or irritating solutions, ointments, or powders. Some are very resistant to any type of treatment and even take skin grafts poorly.

The use of concentrated human blood cells both in the form of the natural gelatinous mass and in the form of dried powder as a topical application arose from the attempt to utilize this by-product of plasma extraction. There is considerable evidence that healing processes are promoted by blood cells. Nature provides a crust of clotted blood over lacerations and abrasions of the skin. Under this crust granulation and epithelization progress. The crust undoubtedly serves as a protection from exogenous contamination and may be a nutritive supply for the reparative process. Dentists dread the occurrence of "dry sockets" following extractions, in which there is no clot to organize, contract,

Received for publication April 20, 1916

*Fellow in Medicine, Mayo Foundation

†Division of Medicine, Mayo Clinic

‡Section on Anesthesiology, Mayo Clinic

and fill the defect. Seldon, Lundy, and Essex¹ actually observed accelerated growth of vascular and connective tissue in the rabbit ear in the presence of an old hemorrhage.

Naide² reported promising results in eleven of fifteen cases in which he removed blood from the patient's antecubital vein and allowed it to clot in an ulcer crater. Moorhead and Unger³ first used as a dressing for ulcers the gelatinous mass of concentrated human blood cells from which the plasma had been extracted. They were impressed by the decrease of purulent secretion, stimulation of healthy granulations, and the impervious covering which was created.

Difficulty was experienced in the handling of human blood cells in their wet form in their early use at the Mayo Clinic. For that reason one of us (T. H. S.) proposed the use of dried and powdered human blood cells. In an earlier report, Seldon and Young⁴ outlined the method of preparation and technique of application. As a result of these and subsequent observations, it was felt that the favorable effects of dried and powdered blood cells in the healing of wounds and ulcers were due to some nutritive factor within the cells which is more or less specific in its action.⁴⁻⁶

Murray and Shaar⁷ prepared a paste of red cells with tragacanth and hexyl-resorcinol. They observed more constant relief of pain with this mixture than with the powdered form. In addition to the nutritive and protective property hypothesized by other observers, they expressed the idea that the crust also serves as a mechanical scaffolding to support epithelization.

It is our purpose in this publication to attempt an evaluation of the efficacy of powdered human blood cells in the treatment of chronic ulcers of patients admitted to the hospital service for peripheral vascular diseases. All of the patients had definite vascular insufficiency as the basis for the ulcerations. The patients were entirely unselected in that they included all those treated with blood cells over a period when they came under the observation of one or all of us.

Needless to say, a controlled study comparing the results of various forms of local treatment for vascular ulcers of human beings is an impossibility since no two patients present lesions of identical size, duration, and character with identical underlying vascular pathologic changes. Conclusions must, therefore, be based largely on the clinical impression of the physician who has seen and treated similar patients. In many cases it was possible to compare the effect of powdered blood cells with that of other topical applications which had been used previously during the period of hospital treatment for the same patient.

MATERIAL AND METHOD

The series to be presented here includes forty-six patients divided primarily into two groups on the basis of the underlying vascular disease. In twenty-nine patients arterial insufficiency was the primary vascular factor, and in the remaining seventeen, venous insufficiency was the primary factor. A further breakdown of the cases into specific vascular diseases gives the following distribution: thromboangiitis obliterans, sixteen; arteriosclerosis obliterans, thirteen; post-thrombophlebitic venous insufficiency, ten; varicose veins with venous

TABLE 1. THROMBOANGITIS OBLITERANS

CASE	AGE (YR.) AND SEX	DURATION VASCULAR DISEASE (YR.)	DURATION OF VASCULAR DISEASE (MO.)	SIZE OF ULCER (CM.)	LOCATION OF ULCER	DESCRIPTION OF ULCER	PREVIOUS TREATMENT	DURATION OF POWDERED BLOOD CELL TREATMENT (DAYS)	COMMENT
1	44 M	8	24	1 by 0.8 1 by 0.8	Dorsum R2 and 3 toes	Infected and ischemic	Various ointments, boric acid dressings	15	Good result; 75 per cent healed
2	55 M	17	4	1 by 0.5 1 by 1	R2 toe	Gangrenous and deep	Boric acid soaks, sulfathiazole ointment, tyrothricin dressings	34	Fair result; healed to bone exposed in base; osteomyelitis of phalanx
3	38 M	1	2	1.5 by 1	Subungual R1 toe	Crusted and oozing	Boric acid soaks, nail removed, tyrothricin dressings	9	Fair result; practically healed
4	36 M	2	2	1 by 1	Plantar L1 toe	Indolent and gangrenous	"Callus cure," sulfathiazole ointment, tyrothricin dressings	23	Continued necrosis; guillotine amputation of L1 toe; 0.5 by 0.5 cm. residual ulcer healed in seven days with blood cells
5	52 M	10	3	Small	Web between L4 and 5 toes	Fissure, pale and ischemic	Fungicide, various ointments, potassium permanganate soaks	18	Good result; ulcer healed
6	55 M	4	3	2 by 3	Dorsum L foot	Deep and gangrenous	Boric acid and tyrothricin dressings	27	Fair result; ulcer healed; blood cells used alternately with boric acid soaks
7	25 M	3	9	2 by 2	L5 toe	Gangrenous	Chemical cautery, sulfathiazole ointment, debridement	11	Good result; practically healed

8	35 M	2	1	2 by 2	R1 toe	Deep and necrotic	Various ointments, roentgen therapy, boric acid and tyrothricin dressings	20	Good result; healed
9	47 M	9	108	2.5 by 2	R1 toe	Irregular gray exudate	Fungicide, various ointments, boric acid and potassium permanganate soaks	23	Good result; healed
10	43 M	5	4	Small (3)	R5 toe R4 toe R3 and 4 toes	Infected and superficial	Fungicides, boric acid and potassium permanganate soaks	30	Good result; healed
11	45 M	10	8	5 by 3	R1 toe and foot	Purulent and ischemic	Removal of metatarsal bone, guillotine amputation R1 toe, tyrothricin dressings	28	Good result; almost healed
12	49 M	4	24	1.5 by 1.5	R1 toenail bed	Deep and necrotic	Curettage, tyrothricin dressings	19	Good result; ulcer healed
13	38 M	8	4	3.8 by 2.5	L ankle	Indolent, stasis	Boric acid dressing	10	Good result; ulcer healed
14	29 M	4	2	1 by 1	R1 toe	Infected and ischemic	Boric acid and tyrothricin dressings; sequestrum removed	19	Good result; ulcer healed
15	33 M	1½	6	3.5 by 2.5	L foot and L5 toe	Gangrenous; osteomyelitis of 5 metatarsal	Sulfathiazole ointment, boric acid soaks	58	Fair result; ulcer healed
16	29 M	8	1½	3 by 3	R1 toe amputation site	Gangrenous	Boric acid and tyrothricin dressings	35	Fair result; 80 per cent healed; rapid progress on dismissal

TABLE II. ARTERIOSCLEROSIS OMLITERANS

CASE	AGE (YR.) AND SEX	DURATION VASCULAR DISEASE (YR.)	DURATION OF ULCER (MO.)	SIZE OF ULCER (CM.)	LOCATION OF ULCER	DESCRIPTION OF ULCER	PREVIOUS TREATMENT	DURATION BLOOD CELL THERAPY (DAYS)	COMMENT
17	63 M	3	1	2 by 2 2 by 2	Dorsum L foot L1 toe	Infected and ischemic	Boric acid and tyrothricin dressing, sulfathiazole ointment	20	Fair result; apparently healed; polycythemia vera
18	60 M	5	3	3 by 3	Amputation site of L4 and 5 toes	Purulent and infected	Amputation of toes, boric acid dressings	17	Fair result; ulcer healed to exposed bone; osteomyelitis of 4 metatarsal; polycythemia vera
19	58 M	1	1	0 5 by 0 5 0 2 by 0 2	R2 and 5 toes	Ischemic and dirty	Various ointments, boric acid soaks	15	Fair result; ulcer 2 toe healed; ulcer 5 toe improved; diabetes mellitus; polycythemia vera
20	55 M	5	24	Multiple small and large	R and L lower legs	Circumscribed, deep, infected	Tyrothricin dressings	30	Fair result; all ulcers healed; polycythemia vera with stasis
21	35 M	2	1 1/4	1 by 1	Bursa L1 toe	Necrotic	None	9	Fair result; tiny persistent opening into bursa
		3	2	1 by 1	L ankle	Crusted and necrotic	Boric acid dressings	14	Fair result; definite healing
		4	2	2 5 by 2 1 2 by 1	L foot and shin	Deep and necrotic	Boric acid and penicillin dressings	30	Fair result; two small ulcers healed; large ulcer 30 per cent healed

22	63 M	15	5	6 by 3.5	R knee	Gangrenous, foul slough	Sequestrectomy, various ointments, boric acid and tyrothricin dressings	108	Good result; ulcer healed; severe ischemia
23	57 M	8	10	3.8 by 3	L shin	Indolent, deep, infected	Various ointments, boric acid and tyrothricin dressings	9	Good result; 66 per cent healed
24	71 M	2	3	1 by 1	L1 toe	Osteomyelitis L1 toe, infected	Nail removed, boric acid dressings	5	Good results; healed except for pin-hole sinus
25	44 M	2	2	1 by 1	L1 toe	Gangrenous	Chirobody, boric acid soaks, sulfathiazole ointment	8	Fair result; improved
26	54 M	1	12	5 by 10	L ankle	Deep, painful, infected	Various ointments, boric acid dressings	40	Good result; practically healed
27	64 F	1/4	3	1 by 1.5 1 by 1	L and R ankles	Blue and painful	Various ointments, tyrothricin dressings	7	Fair result; 80 per cent healed
28	47 M	1/6	2	3 by 3 by 2	R foot, plantar	Deep and necrotic	Boric acid dressings	25	Good result; ulcer healed; diabetes mellitus
29	61 M	15	1	1.5 by 1.5	R1 metatarsal	Large, deep necrotic	Boric acid and tyrothricin dressings, sulfathiazole ointment	89	Poor result; some improvement; base of ulcer on joint capsule; diabetes mellitus

TABLE III. VENOUS INSUFFICIENCY—RESIDUAL OF PREVIOUS THROMBOPHLEBITIS

CASE	AGE (YR.) AND SEX	DURATION VASCULAR DISEASE (YR.)	DURATION ULCER (MO.)	SIZE OF ULCER (CM.)	LOCATION OF ULCER	DESCRIPTION OF ULCER	PREVIOUS TREATMENT	DURATION BLOOD CELL THERAPY (DAYS)	COMMENT
30	52 F	15	4	5 by 3	L medial malleolus	Infected and irregular	Various ointments, boric acid dressings	10	Good result; ulcer healed
31	42 M	14	3	Large	R shin	Infected and irregular	Long saphenous ligation, boric acid dressings	4	Good result; slow healing with boric acid; accelerated with blood cells
32	42 F	14	12	5 by 2 5	R medial malleolus	Indolent, infected	Attempted skin graft, long saphenous ligation	24	Good result; ulcer healed
33	46 F	23	23	2 by 2 2 by 1	L and R ankles	Indolent	Various ointments, long saphenous ligation	13	Good result; ulcers healed
34	70 F	2	2	11 by 16	R ankle	Indolent, superficial	Attempted skin graft, boric acid dressings	8 5	Poor result; generalized eczema developed

35	48 F	17	8	3 by 3	L ankle	Ragged, purulent plug	Boric acid and tyrothricin dressings	4	Fair result; apparently healed; ulcer was healing slowly with blood dressings
36	37 F	21	7	2 by 2	L ankle	Infected and irregular	Long saphenous ligation, boric acid and tyrothricin dressings	11	Good result; ulcer healed
37	38 M	16	5	3 by 2	L ankle	Indolent, gray slough	Boric acid and tyrothricin dressings	19	Good result; ulcer healed
38	42 M	28	5	15 by 10	L ankle	Painful, deep and foul	Various ointments, tyrothricin dressing	10 14	Fair result; ulcer granulating well; graft applied; marginal ulcers responded to blood cells
39	55 F	3	1½	3 by 3	R calf	Chronic and infected	Boric acid dressings, various ointments	30	Fair result; 90 per cent healed

TABLE IV. PRIMARY VARICOSE VEINS WITH VINOR'S INSUFFICIENCY

CASE	AGE (YR.) AND SEX	DURATION VASCULAR DISEASE (YR.)	DURATION OF ULCER (MO.)	SIZE OF ULCER (CM.)	LOCATION OF ULCER	DESCRIPTION OF ULCER	PREVIOUS TREATMENT	DURATION BLOOD CELL THERAPY (DAYS)	COMMENT
40	31 F	14	3	10 by 10	R ankle	Superficial and irregular	Boric acid dressings	6	Good result; ulcer healed
41	52 M	25	3	2 by 2 by 1	L ankle	Irregular and infected	Various ointments, boric acid and tyrothricin dressings	9	Fair result; ulcer improved—completed in ten days with boric acid and tyrothricin dressings
42	16 F	25	25	6 2 by 3 8	L ankle	Ragged, foul discharge	Long saphenous ligation, various ointments	28	Good result; ulcer healed
43	56 M	33	33	3 by 3 0 5 by 0.5	R and L ankles	Deep and jagged	Attempted skin graft, paste boots, various ointments	30	Fair result; small remaining ulcer healed after saphenous ligation
44	30 M	8	8	4 "large" ulcers	R and L ankles	Punched out, infected	Bilateral long saphenous ligation, boric acid dressings	6	Fair result; good granulation; graft applied
45	59 F	30	25	Large (6 by 8) 2 by 4	R shin L ankle	Irregular and deep	Long saphenous ligation, boric acid and tyrothricin dressings	27-L 23-R	Good result; almost complete healing
46	37 M	13	13	2 by 5	R ankle	Infected and dirty	Various ointments, boric acid dressings	6	Fair result; 50 per cent healed

insufficiency, seven. Diabetes mellitus complicated three and polycythemia vera four of the cases of arteriosclerosis obliterans.

Cultures were obtained from only fifteen ulcers. *Streptococcus hemolyticus* and *Staphylococcus aureus* grew in three cases (Cases 9, 10, and 44); *Staph. aureus* alone from six ulcers (Cases 15, 21, 27, 28, 37, and 45); *Str. hemolyticus* alone in one (Case 11); and *Escherichia coli* alone in one (Case 26). The other four cultures contained, respectively, diphtheroids, micrococcus, pseudomonas, and combined *Staph. aureus* and *Streptococcus viridans* (Cases 14, 20, 21, and 34).

On admission to the hospital, nearly all of the patients exhibited a certain degree of local cellulitis, active exudation, or gangrenous slough in or about the ulcer. Initial therapy to clean up the ulcer and surrounding tissue consisted usually of either soaks or dressings of warm saturated solution of boric acid or 0.5 per cent tyrothricin dressings. In a few cases potassium permanganate soaks (1:10,000 dilution), irrigation with penicillin solution, or application of 5 per cent sulfathiazole ointment was used for this same purpose. Many patients not included in this series showed good response to these measures, which were then continued, and local application of powdered blood cells was not used. For this reason, the ulcers which were treated with powdered blood cells were those which proved resistant to the usually accepted hospital regimen.

All patients received treatment which was aimed to relieve the underlying vascular disease. Those patients who had occlusive arterial disease were treated with rest in bed, warm environmental temperatures, and the Sanders oscillating bed. The use of tobacco was forbidden. Typhoid vaccine and lumbar sympathectomy were auxiliary vasodilating procedures employed in several cases of thromboangiitis obliterans. Phlebectomy and phenylhydrazine therapy supplemented local treatment in patients with complicating polycythemia vera. Diabetes mellitus when present was treated with diet and insulin. When venous insufficiency was the underlying factor, the involved extremities were kept elevated. Orally administered sulfadiazine or parenterally administered penicillin was used to treat spreading local infection whenever indicated.

Minor surgical procedures, such as removal of sequestra in underlying osteomyelitis and removal of nails in subungual lesions, were performed to give better exposure of the ulcers for local therapy (Cases 3, 4, 7, and 24). Two of the ulcers in patients with thromboangiitis obliterans were at the site of guillotine amputation for gangrenous toes (Cases 11 and 16). Blood cells were applied as adjuncts before and after skin grafting in two patients (Cases 38 and 44).

The mode of application and the method for preparing the powdered human blood cells were similar to those outlined in earlier reports from the Mayo Clinic.⁵ After the ulcer had been cleaned with wet dressings, the powdered blood cells were applied with a sterile spatula or swab or dusted on from a container with a shaker top. The entire surface of the ulcer was covered with the powder and then loosely covered with a dry sterile dressing. Exudate absorbed from the tissues caused the powder to form a hard crust resembling that seen commonly on traumatic abrasions. Sometimes seepage from the ulcer caused the cell

crust to stick to the dressing and this was gently removed once daily. Any remaining serum was gently sponged from the bed of the ulcer with sterile sponges and a new layer of blood cells was applied. Eventually, as healing progressed, a point would be reached where the crust no longer stuck to the dressing. Then it was allowed to remain intact unless there was evidence of exudate underneath, which prevented contact between the cells and the bed of the ulcer. In these cases, the crust was loosened by soaking in boric acid solution or by applying dressings moistened with boric acid solution and was removed with a sterile forceps, and more powdered blood cells were applied. When healing was complete, the crust was either allowed to fall off spontaneously or was soaked until it softened enough to be peeled off.

RESULTS

Data concerning the cases in which powdered blood cells were used and results of this treatment are given in Tables I, II, III, and IV. In the final column is listed the condition of the ulcer at the time the patient was dismissed from the hospital or at the time powdered blood cell therapy was discontinued.



Fig. 1 (Case 12).— *a*, Thromboangiitis obliterans with gangrenous ulcer of bed of right first toenail. The ulcer had been present for two years. No evidence of healing was noted during local treatment with tyrothricin, after intravenous administration of typhoid vaccine, or after lumbar sympathectomy. *b*, Same ulcer almost healed seven days after treatment with powdered blood cells was begun. The ulcer was completely healed on the nineteenth day of treatment.

The results in those patients who left the hospital before complete healing occurred and who were given cells and instructions in their use at home are listed as percentage of ulcer healed (Cases 1, 11, 16, 21, 23, 27, and 46). Complete healing was prevented in some cases by the presence of exposed bone or a persistent sinus tract in the base of the ulcer (Cases 2, 18, 21, and 24). In two cases, powdered blood cells were used preoperatively and postoperatively where large defects were covered with split-thickness skin grafts (Cases 38 and 44). Treatment

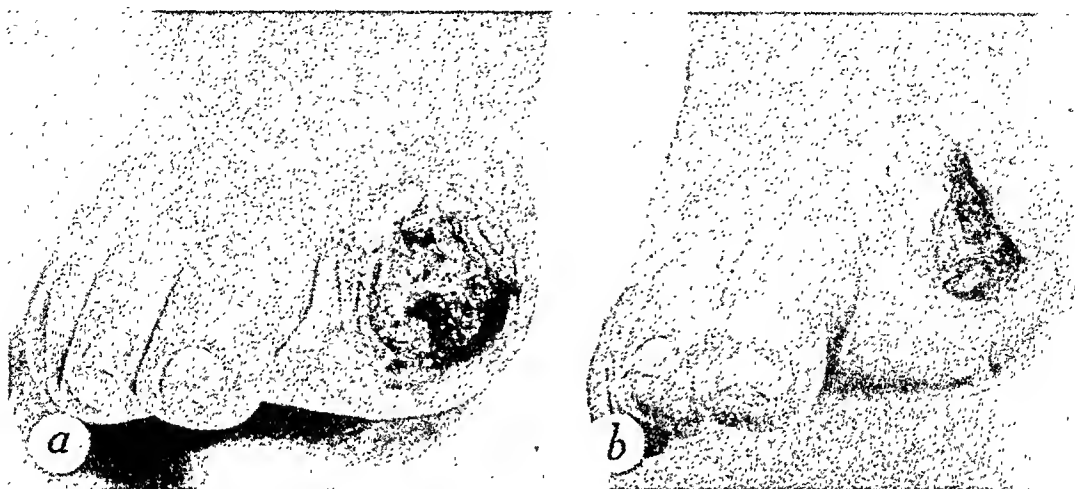


Fig. 2 (Case 16).—*a*, Thromboangiitis obliterans with ulcer at site of amputation of right first toe for gangrene. The patient had previously undergone lumbar sympathetic ganglionectomy. The ulcer was very painful and had failed to show any evidence of healing when treated with warm boric acid soaks, boric acid dressings, and tyrothricin during a period of six weeks. *b*, Same ulcer after treatment with powdered blood cells for thirty-five days. Pain was relieved and ulcer was 80 per cent healed.



Fig. 3 (Case 11).—*a*, Thromboangiitis obliterans with deep gangrenous ulcer at site of amputation of right first toe and removal of distal half of right first metatarsal. The ulcer had been present for eight months. Tyrothricin wet dressings had been ineffective. *b*, Same ulcer almost completely healed after treatment with powdered blood cells for twenty-eight days.



Fig. 4 (Case 28).--*a*, Arteriosclerosis obliterans with diabetes mellitus and infected ulcer in large callus over plantar surface of fifth metatarsal head. The ulcer had been present for two months. *b*, Same ulcer completely healed thirty-one days after treatment with powdered blood cells had been begun.



Fig. 5 (Case 42).--*a*, Primary varicose vein with chronic venous insufficiency and ulcer which had been present for more than two years. No healing had followed ligation and sclerosis of long saphenous vein and tributary varices. *b*, Same ulcer healed twenty-seven days after treatment with powdered blood cells had been started.

with powdered blood cells was discontinued in one case of stasis ulceration because of poor results (Case 34). In this patient severe generalized dermatitis developed. Powdered blood cells failed to control gangrenous ulceration in one patient with thromboangiitis obliterans in which guillotine amputation of a toe was required. Subsequently, the site of amputation healed rapidly during treatment with powdered blood cells (Case 4). Figs. 1 to 6, inclusive, show the results of treatment.

On the basis of observation on the progress of healing, Table V summarizes the results in the various types of vascular disease. In this table, good results

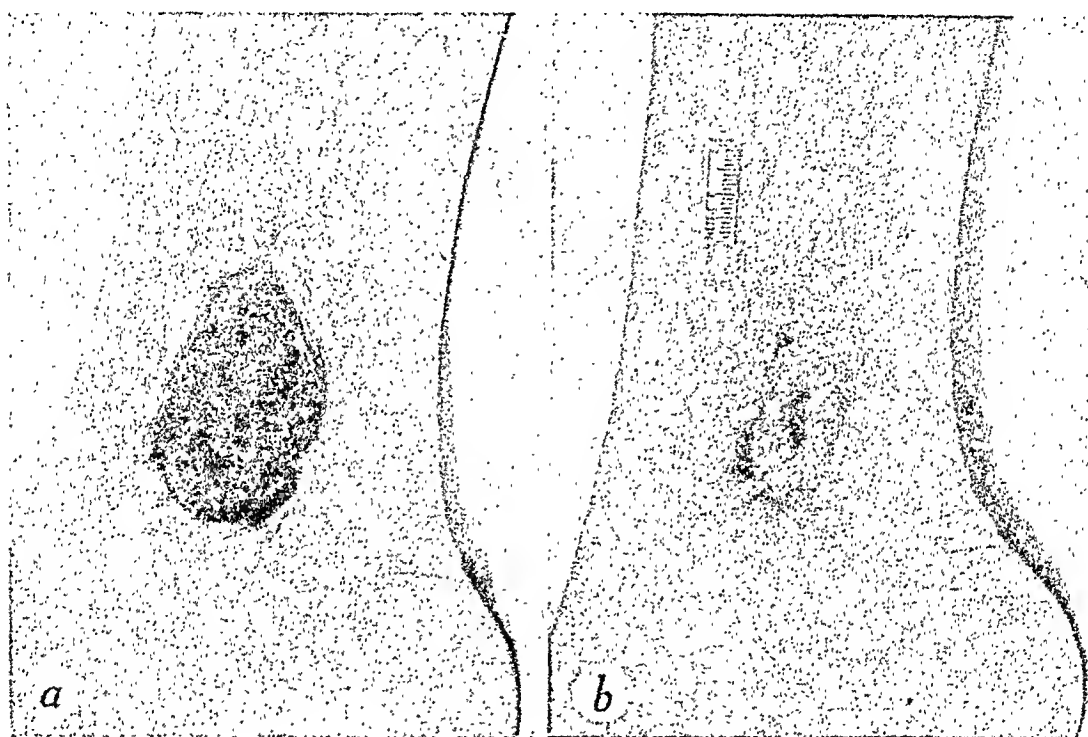


Fig. 6 (Case 32). —*a*, Chronic venous insufficiency caused by ancient iliofemoral thrombophlebitis with large ulcer of one year's duration at site of two previous ulcers. Attempted skin graft had failed one month before this picture was taken. *b*, Same ulcer healed twenty-four days after treatment with powdered blood cells had been started.

TABLE V. RESULTS OF TREATMENT WITH POWDERED BLOOD CELLS

DISEASE	CASES	RESULTS		
		GOOD	FAIR	POOR
Thromboangiitis obliterans	16	10	5	1
Arteriosclerosis obliterans	13	5	7	1
Post-thrombophlebitic venous insufficiency	10	6	3	1
Varicose veins with venous insufficiency	7	3	4	0
Totals	46	24	19	3

indicate that the powdered blood cells appeared to be superior to other local applications. Fair results indicate that the ulcers healed but probably not more rapidly than might have been expected with other local applications. Poor results indicate failure to heal or intolerance to treatment with powdered blood cells.

COMMENT

The use of powdered human blood cells as a topical application for chronic ulcers of the extremities associated with vascular disease is one of several methods of bland and nonirritating local treatment available to the physician. In order to evaluate its effect, we have reviewed a series of cases in which the patients were treated by this method at the Mayo Clinic. Despite the fact that patients with ulcers associated with venous insufficiency are more frequently seen on the hospital service than are those with ulcers associated with other types of vascular disease, fewer of these received this form of treatment since they frequently responded well to other bland local applications.

It is our impression that in approximately one-half of the patients with both the ischemic ulcers and stasis ulcers treated with the powdered blood cells, healing was much accelerated. This is based on previous experience with similar ulcers in patients with comparable degrees of vascular disease in whom other methods of local treatment were used and in those in whom a prolonged trial of other local applications had been made without evidence of healing before the powdered blood cells were used. In approximately one-half of the patients in whom powdered blood cells were used, it is questionable whether healing occurred any more rapidly than it would have with other bland local applications. In a few patients less healing occurred or the treatment was not well tolerated. Occasionally, it was necessary to alternate for periods of a few days treatment with powdered red blood cells and treatment with bland wet dressings or tyrothricin solution.

It is difficult to determine whether the favorable response occurs from partial desiccation, from some healing factor in the cells, from nutrition supplied by the crust, or merely because the crust is protective and entirely nonirritating. Nevertheless, it is encouraging to observe progress in the ulcers, with first a puckering of the surrounding skin, then a freshening and reddening of the gray, avascular base, and finally granulations with epithelium creeping in from the margins. Certain disadvantages of wet dressings, such as maceration of the skin and chilling, are avoided with this "dry" method of treatment.

Care is necessary in removing the crusts and in applying the new dressing each day but, once the dressing has been applied, it need not be touched for twenty-four hours or sometimes longer. This has the advantage of simplicity and requires little time. Painful ulcers may become a little more painful during the first day the powdered blood cells are applied. After that, pain is usually relieved. Naturally, the use of blood cells in dealing with vascular ulcers is supplementary to the use of treatment to improve circulation and not a substitute for it.

REFERENCES

1. Seldon, T. H., Lundy, J. S., and Essex, H. E.: Effect of Certain General Anesthetic Agents on the Small Blood Vessels in the Ear of the Rabbit, *Anesthesiology* 3: 146, 1942.
2. Naide, Meyer: Treatment of Leg Ulcers With Blood and Concentrated Plasma, *Am. J. M. Sc.* 205: 489, 1943.
3. Moorhead, J. J., and Unger, L. J.: Human Red Cell Concentrate for Surgical Dressings, *Am. J. Surg.* 59: 104, 1943.
4. Seldon, T. H., and Young, H. H.: Use of Dried Red Blood Cells in Wound Healing, *Proc. Staff Meet., Mayo Clin.* 18: 385, 1943.
5. Seldon, T. H., Lundy, J. S., and Adams, R. C.: Powdered Erythrocytes for Dressing of Wounds and Ulcers, *S. Clin. North America* 24: 814, 1944.
6. Seldon, T. H., Lundy, J. S., and Adams, R. C.: Stimulation of Wound Healing—New Use for Powdered Red Blood Cells, *Anesthesiology* 5: 566, 1944.
7. Murray, C. K., and Shaar, C. M.: Red Cell Paste in the Treatment of Ulcers and Chronically Infected Wounds, *J.A.M.A.* 125: 779, 1944. .

STUDIES ON THE VASCULARIZATION OF THE AORTA

I. THE VASCULARIZATION OF THE AORTA IN THE NORMAL DOG

J. G. SCHLICHTER*

CHICAGO, ILL.

THE possibility exists that diseases of the aorta are related to disturbances of the vascularization of its wall. This possibility was subjected to an experimental investigation in which (1) the vascularity of the aorta in several species of animals and in man in health and disease was studied by injection with radio-paque material and (2) the effects of experimental interference with this vascularization were analyzed.

In the present report the technique of studying the vascularity of the aorta is presented and the vascularization of the aorta in the normal dog is described.

TECHNIQUE

The hearts and aortas of fifty-seven dogs were obtained post mortem. The aortic vasa vasorum were injected in one of two ways. In the first method a glass cannula was inserted into the aorta, either at the arch or in the descending portion, facing upstream and tied firmly in place. All the branches of the aorta above the cannula except the coronary arteries were tied with catgut near their origin from the aorta. In the second method, one or two of the coronary artery branches, either of the right, of the left, or of both, were cannulated with the cannula facing upstream. Before injecting the coronary branch or branches, the coronary ostia in the sinus of Valsalva and the ascending aorta were occluded by means of wet cotton to prevent leakage into the aorta.

The injection material used was the gelatine-lead carbonate-mercuric sulfide mixture described by Dock.¹ It was injected under a pressure of between 150 to 200 mm. Hg in the various experiments by means of the apparatus developed by Schlesinger.² The aortas were opened and x-rayed; after the tissue was properly fixed, microscopic sections were prepared.† The x-ray technique used was: 40 kv.; 30 Ma.; 1½ sec.; a fine focal spot; anode-film distance, 30 inches; paper film holder and nonscreen film.‡

RESULTS

Ascending Aorta.—This study revealed that the ascending aorta of the normal dog is supplied (1) by vessels arising from the left and right coronary

*From the Cardiovascular Department, Michael Reese Hospital.

†Aided by the A. D. Nast Fund for Cardiovascular Research. This department is supported in part by the Michael Reese Research Foundation.

‡Received for publication May 4, 1946.

§Thanks of the Darwin Foundation.

¶We are indebted to Dr. O. Saphir for the cooperation of the Pathology Department in preparing the microscopic sections.

‡We are indebted to Dr. R. Arenas for the cooperation of the x-ray Department in obtaining the x-ray pictures.

arteries, (2) by vessels arising from the great vessels originating in the aortic arch, namely, the subclavian, carotid, and innominate arteries, and (3) by vasa arising directly from the lumen of the aorta. The vasa from these three sources form a rich anastomotic network (Fig. 1). Since the dye used is too coarse to fill vessels less than 10μ in diameter, the anastomoses observed consist of vessels

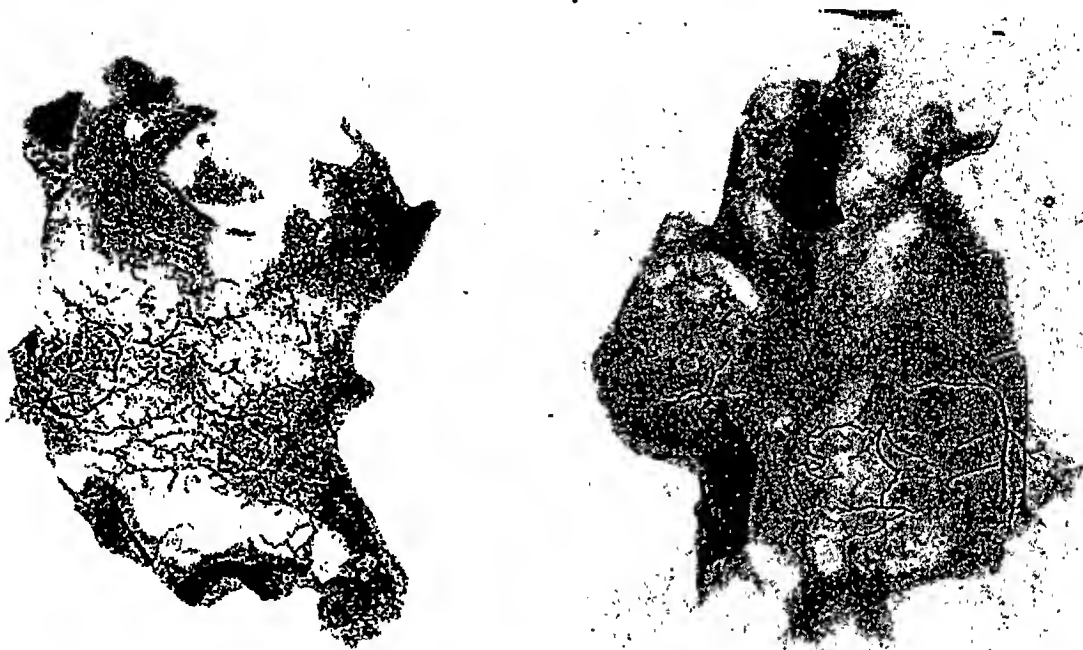


Fig. 1.—Injection of the vasa of the ascending aorta demonstrating their origin from both coronary arteries (below), from the vessels of the arch (above), and directly from the lumen of the aorta. Injection with cannula in the arch of aorta.

Fig. 2.—Injection of the first branches of the coronary arteries which supply the vasa of the ascending aorta.

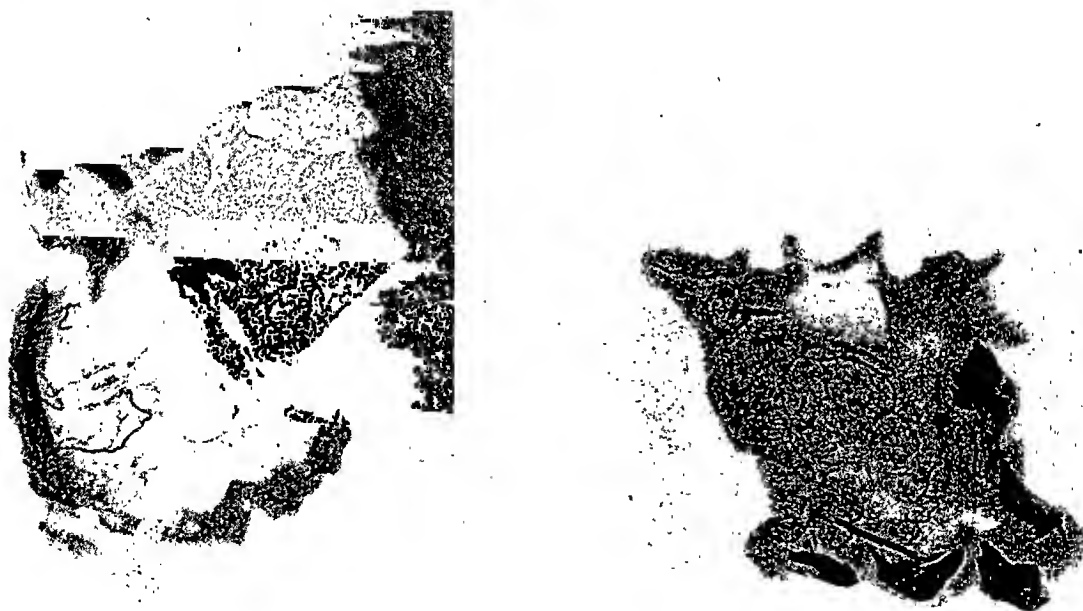


Fig. 3.—Anastomoses between the vasa arising from the right coronary artery and those arising from the left coronary artery. The left coronary artery was occluded at its orifice and the right coronary artery was injected by cannulation.

Fig. 4.—A preparation with an accessory ostium of the right coronary artery (the thick oblique vessel in the lower part of aorta). Note the predominance in the ascending aorta of the vasa arising from this coronary artery.

having three coats. The entire description of the vasa given below will therefore be confined to vessels of 10μ or more in diameter. Analysis soon revealed that the network was made up of (1) an adventitial network and (2) a medial network. The former was found to be far more extensive than the latter.

Adventitial Network: This network is supplied by vessels from the coronary arteries and from the large arteries of the aortic arch.

The first branches of the coronary arteries are the vasa to the aorta and pulmonary artery. These spread upward in the adventitia anteriorly and posteriorly over the ascending aorta. There are rich anastomoses between the branches of the left and right coronary arteries; anteriorly they are located in the region of the aortic-pulmonary groove and over the pulmonary artery; posteriorly they are in the region of the aortic-auricular groove and on the posterior aspect of the aorta (Figs. 1, 2, and 7). As a matter of fact, the anastomoses are so abundant that the vasa of one coronary artery can be filled via the aortic branches of the other coronary artery (Fig. 3).

When accessory ostia of either the left or right coronary artery exist in the sinus of Valsalva, they are the chief origin of the aortic vasa (Fig. 4). It has been stated that the vessels of the dog's aorta arise predominantly from the right coronary artery in most animals.³ However, our findings do not bear this out. Usually no predominance was found in our series except in those instances in which accessory ostia were present (Fig. 4). Actually we found:

No preponderance	45 dogs
Left preponderance	2 dogs
Right preponderance	3 dogs
Accessory ostia	7 dogs, in which there was a right accessory ostium and right preponderance in 5 dogs, and a left accessory ostium and left preponderance in 2 dogs



FIG. 5 - Arterio branches of the left and right coronary artery supplying the root of the aorta and anastomosing with vasa of other origins. Note the direct vessel from the lumen of the aorta in the upper left-hand portion of the aorta.

FIG. 6 - Direct vasa of from the lumen of the aorta. Injection by aortic cannula in the arch with coronary arteries tied off at their orifices.

In addition to the vasa from the coronary arteries described, other vasa to the aorta arise more distally. These are the arcuate branches which supply the aorta and the aortic fat pad (Fig. 5). These arcuate branches anastomose freely with the other aortic vasa.

The other source for the adventitial network of the ascending aorta arises from the large arteries of the aortic arch and from the pericardium, descending

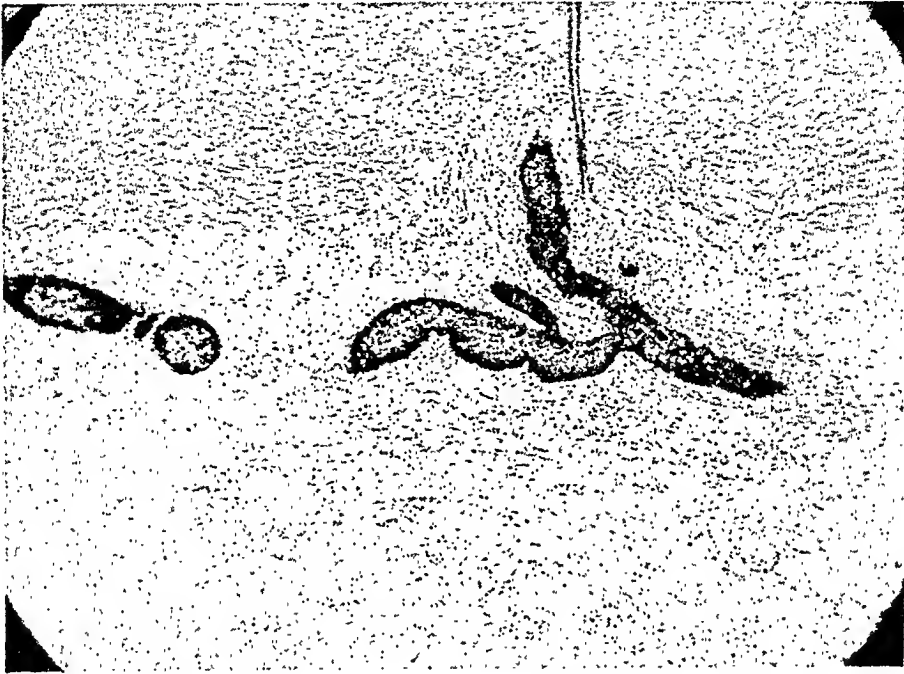


Fig. 7.—Anastomoses in the adventitia. Hematoxylin and eosin stain ($\times 56$).

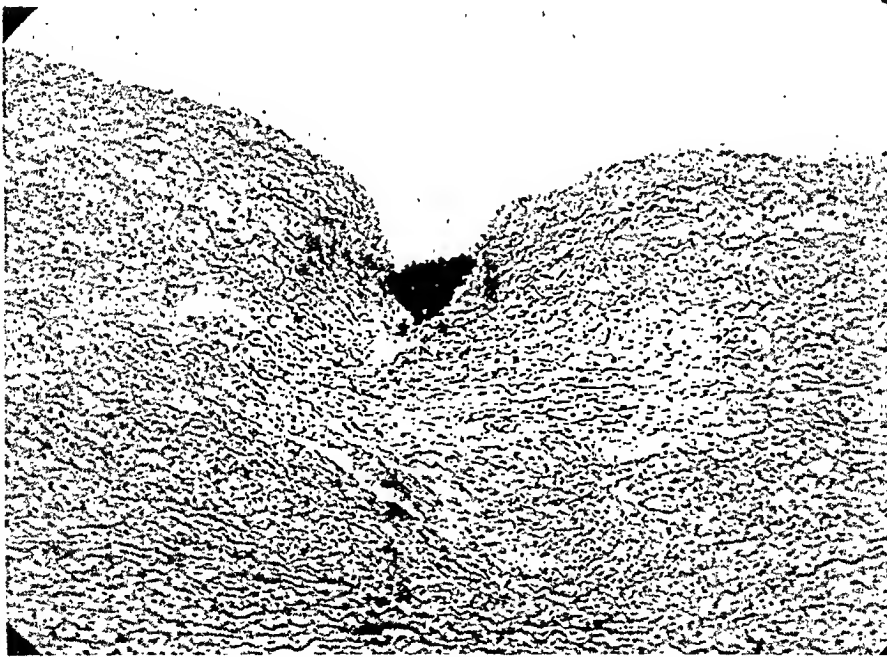


Fig. 8.—Ostium of a direct vessel from the lumen of the aorta filled with dye. Hematoxylin and eosin ($\times 10$).

from the pericardical reflexion. They anastomose extensively with the vasa arising from the coronary arteries as well as from the branches of the bronchial arteries which participate to a slight extent in the supply of the aortic wall near the bifurcation of the pulmonary artery.

Medial Network: The medial network is supplied by branches arising from the adventitial network and by vessels arising from the lumen of the aorta. The former is the more abundant source of supply.

Vasa from the adventitia can be traced as far as the inner third of the media and anastomoses of these medial vessels can be seen in the outer and middle thirds of the media. The vascular supply of the media is not as rich as that of the adventitia (Fig. 7), and the extent of the anastomoses and the number of vasa decrease progressively in the media as the intima is approached. Medial anastomoses occur not only between branches arising from the adventitia but also between these adventitial branches and vessels arising directly from the lumen of the aorta.



Fig. 9.—Direct vessel from the lumen of the aorta which can be followed to the middle third of the media. Hematoxylin and eosin stain ($\times 67$).

When the ascending aorta is opened, small lumina arising in the intima can be seen grossly: in injected specimens, they stand out as red points. These vessels can be followed and their branching traced in the x-ray pictures and in microscopic sections (Figs. 1, 5, and 8). The convincing demonstration that these vessels arise and are supplied from the lumen of the aorta was made in those experiments in which the dye was injected via an aortic cannula in the ascending



Fig. 10.—Direct vessel from the lumen of the aorta anastomosing in the middle third of the media with a vessel arising from adventitial network. Intima above. Hematoxylin and eosin stain ($\times 56$).



Fig. 11.—Stomas and small vessels below 10μ diameter arising directly from the lumen of aorta. Hematoxylin and eosin stain ($\times 204$).

aorta facing upstream and in which the orifices of the coronary arteries had been completely occluded (Fig. 6).

Those vasa arising from the lumen of the aorta spread into the inner and middle third of the media and even reach its outer third and can be seen to anastomose with adventitial vessels (Figs. 9 and 10). On microscopic examination numerous small openings can be seen which are too small in diameter to be injected by the dye (Fig. 11). The larger vessels, 10μ or wider, arising directly from the lumen of the aorta, could not be found in the ascending aorta in dogs having accessory coronary ostia; however, the smaller stomas, below 10μ , were still demonstrable.

Arch and Descending Aorta.—Vessels arising directly from the lumen of the aorta and injectable by the dye used could be demonstrated also in the arch and descending aorta. These vasa and those arising from the large arteries of the aorta are the origin of the adventitial and medial plexuses of the arch and descending aorta. The adventitial plexus becomes progressively less extensive as one progresses from the ascending to the descending aorta. On the contrary the number of intimal vessels increases progressively along the downward course of the aorta.

DISCUSSION

The present study has demonstrated that there is an extensive and elaborate vascular supply to the aorta, richest in the ascending aorta. Its origin is from branches of the aorta, which give rise to an adventitial and a less extensive medial plexus, and from intimal vessels, many of which are more than 10μ in diameter. As the adventitial plexus becomes less and less extensive in going downstream, the number of vessels arising from the intima increase, thus ensuring an adequate blood supply to the aortic wall.

The presence of vasa in the aortic wall had been demonstrated by Robertson.³ Discreet openings in the lumen of the aorta were previously noted by Woodruff⁴ in two dogs. Winternitz and co-workers⁵ injected small stomas in the lumen of the aorta with India ink and found an intimal plexus by this means. However, it is not established that this India ink injected plexus constitutes a capillary vascular plexus. It may represent a network of intercellular spaces into which the highly diffusible India ink was forced by the injection method. When a coarser injection mass is employed, as in the present study, no intimal plexus can be demonstrated. The only vessels, of 10μ or more, found in the intima were vessels running from the lumen to the media. The nourishment of the intima is thus dependent upon diffusion from the lumen of the aorta, from the medial vascular plexus, and from the scattered intimal vasa. Whether or not this is supplemented by a capillary network within the intima must remain undecided.

SUMMARY

1. The vascularity of the aorta in fifty-seven normal dogs was studied by an injection technique which disclosed the presence of vasa $10\ \mu$ or more in diameter.
2. An elaborate system of vasa was found consisting of an extensive adventitial plexus and a less extensive medial one.
3. These plexuses are supplied by vessels arising from the coronary arteries and the larger arteries originating from the arch of the aorta. In addition, vasa arising from the lumen of the aorta course through the intima to join the plexuses; the number of these aortic intimal vasa increases progressively caudad.

I am greatly indebted to Dr. Louis N. Katz for his guidance and suggestions during the progress of this investigation.

REFERENCES

1. Dock, W.: J. Exper. Med. 74: 177, 1941.
2. Schlesinger, M. J.: AM. HEART J. 15: 528, 1938.
3. Robertson, H. F.: Arch. Path. 8: 881, 1929.
4. Woodruff, C. E.: Am. J. Path. 2: 567, 1926.
5. Winternitz, M. C., Thomas, R. M., and LeCompte, P. M.: The Etiology of Arteriosclerosis, Springfield, Ill., 1938, Charles C. Thomas.

Clinical Reports

RIGHT-SIDED AORTA WITH ATYPICAL COARCTATION INVOLVING ONLY THE LEFT SUBCLAVIAN ARTERY. HYPERTENSION

CAPTAIN ARTHUR M. MASTER
MEDICAL CORPS, UNITED STATES NAVAL RESERVE

THE case to be described concerned a young man, J. C. O., 22 years of age, Seaman, first class, in the Navy. He had been healthy all his life and indeed athletically inclined. At college he had played tackle on the freshman and varsity football teams. While attending a midshipman school in the Navy he was examined for promotion but was found physically unfit for a commission as ensign because of hypertension. On March 14, 1945, he was admitted to a U. S. Naval Hospital to appear before a board of medical survey for observation and report.

The young man was asymptomatic. Physical examination disclosed a person of unusually fine physique, who was tall and weighed 175 pounds. There were a few physical observations of note. Over the base of the heart a short systolic murmur was heard. The heart rate was slow, usually ranging from 45 to 60 beats per minute. The left radial pulse was definitely weaker than the right. In fact the pulsations in the brachial, axillary, and carotid arteries of the left upper extremity were smaller than the corresponding arteries of the right side. The blood pressure in the right arm was moderately but definitely elevated; the readings were 158-170/60-76. The pressures in the left arm were normal, 104-124/70-80. The definite abnormalities were therefore the small left radial pulse and the hypertension in the right arm.

The routine laboratory tests were not of significance. The Kahn was negative. Kidney function was excellent. An electrocardiogram disclosed a sinus bradycardia, the rate being about 42 beats per minute (Fig. 1).

The hypertension in an upper extremity, particularly in a young man, suggested the diagnosis of coarctation of the aorta. This diagnosis was dismissed, first, on clinical grounds and, second, by x-ray film of the chest. There was no abnormal relationship of the blood pressure in the upper and lower extremities,^{1,2} no delay in rise or force of the femoral pulse, and no sign of collateral circulation in the chest wall, anteriorly or posteriorly, on inspection or by palpation. Nor did an x-ray film (Fig. 2) give any evidence of erosion of the ribs by dilated intercostal arteries serving as collateral circulation.

The blood pressure in the lower extremities was not decreased but presented the customary elevation above that obtained in the upper limbs. The right thigh arterial tension was 200/100 and the left femoral blood pressure was 200/90.

Pulse tracings of the right radial artery compared with that of either of the femoral arteries confirmed the clinical impression that there was no retarda-

The opinions and views set forth in this article are those of the writer and are not to be considered as reflecting the policies of the Navy Department.

Received for publication Nov. 11, 1945

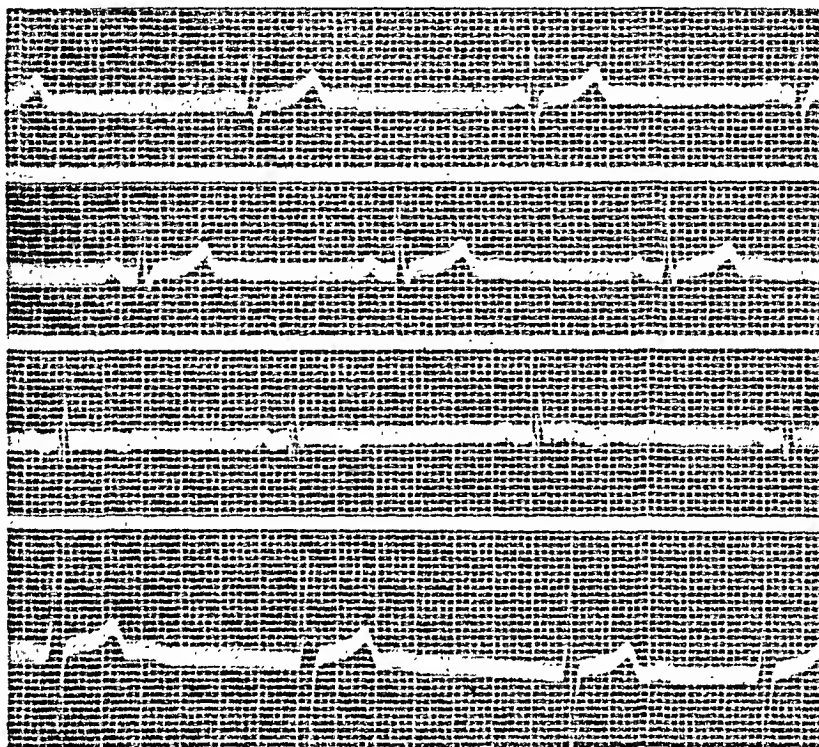


Fig. 1.—Electrocardiogram shows no abnormality. A sinus bradycardia is present; rate, about 45 beats per minute.

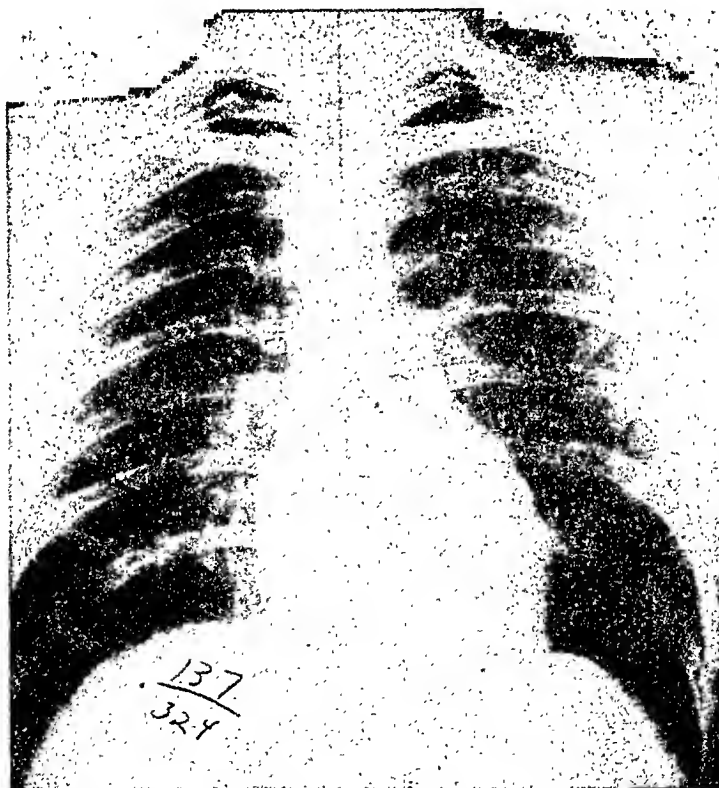


Fig. 2.—Teleroentgenogram reveals a normal globular-shaped heart. The aorta and aortic knob are on right side instead of on left.

tion of the pulses in the lower extremities. In typical coarctation of the aorta, Lewis² observed an average delay of 0.03 second in the pulse of the femoral artery.

The same teleroentgenogram of the chest which aided in disposing of the diagnosis of coarctation of the aorta disclosed a right-sided aorta (Figs. 2 and 3). The diagnosis of this congenital lesion was confirmed by fluoroscopy. The ingestion of the barium mixture revealed the esophagus, at the level of the aortic arch, to be displaced anteriorly and to the left of the aorta instead of being behind this structure (Fig. 3).



Fig. 3 - Lateral view film discloses barium-filled esophagus anterior to the arch of the aorta. Normally the esophagus is behind the aorta.

Although the diagnosis of right-sided aorta was definite, this still did not explain the *diminished left radial pulse* (Fig. 4) nor the hypertension in the right arm. To explain the small pulse in the left forearm a search was made for a left cervical rib. None was present in X-ray films of the chest. Nor was there any variation in the course of the left radial artery. The left upper extremity was completely normal in all other respects. The color and temperature were good. The grip of the left hand was just as powerful as that of the right.

We now considered two congenital anomalies of the left subclavian which could explain the decreased pulse of the left arm. A left subclavian artery has been known to originate on the right side in right-sided aorta and to be compressed in its long path to the left thorax.¹ Also a localized coarctation of the left subclavian artery, such as was recently described by Grishman, Sussman, and Steinberg,³ would be as plausible an explanation. These investigators used the angiocardiographic technique which they have advanced so successfully. We therefore decided that diodrast injection would elucidate the problem. Several

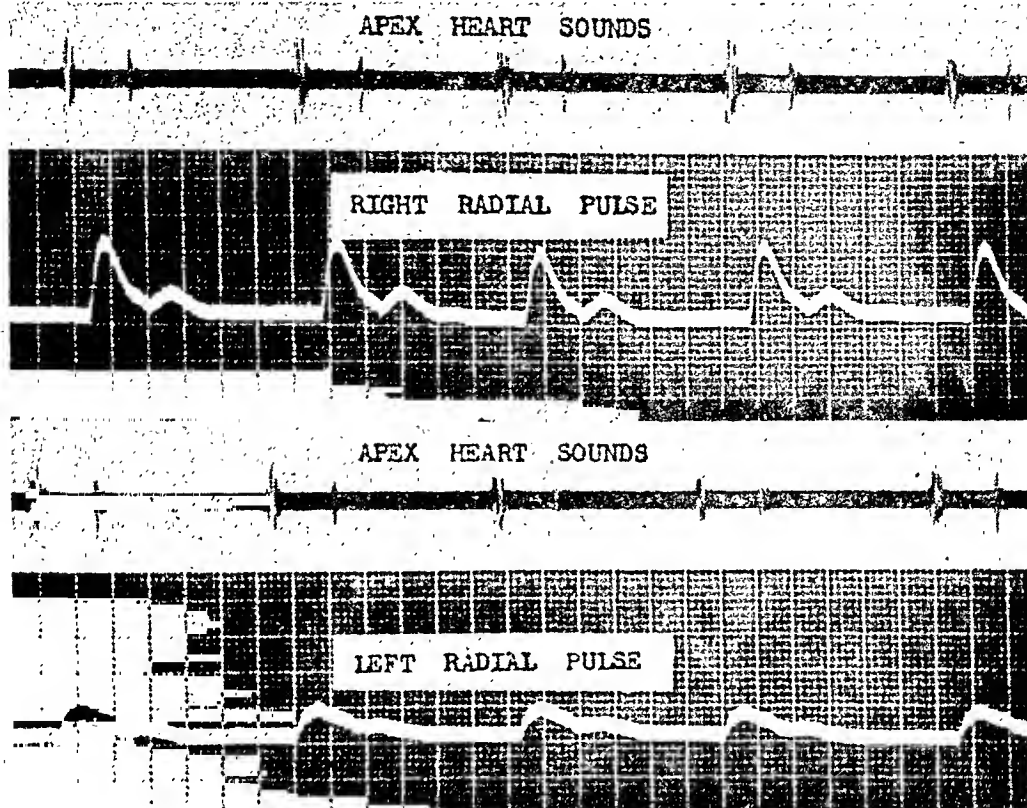


Fig. 4.—Phonocardiogram taken at the apex and pulse tracings of both radial arteries. The left pulse is distinctly smaller than the right and more gradual in its rise.



Fig. 5.—Angiocardiogram demonstrates a right ventricular filling with the diodrast substance passing valves of pulmonary artery. The septum is more convex than usual, probably indicating a hypertension in the left ventricle. (The cavity of this chamber appears to be increased in size.)

angiocardiographic studies were made.* In the first (Fig. 5), the diodrast is in the right ventricle and pulmonary artery. The latter is of normal size and its valves are visible. The cavity of the left ventricle which is not filled with diodrast appears to be increased in size and the ventricular septum appears to be more convex than usual, both of these findings being the result of the hypertension in the aorta.

Fig. 6 is an illustration of the opaque solution in the right ventricle, pulmonary artery, and the right and left branches of this vessel.



Fig. 6 - Angiocardiogram reveals the diodrast entering the left and right pulmonary arteries.

The final diodrast film (Fig. 7) shows the substance in the left ventricle and clearly in the aorta and in the right innominate and the left carotid arteries. There is no sign of the left subclavian artery. This latter vessel was atresic. The small left radial pulse was thus accounted for by a narrowed left subclavian artery. The aorta itself was normal in size and "measured 2.6 cm. in the suprasternal region, 2.5 cm. at the arch and about 2.1 cm. in the descending portion." There was no sign of hypoplasia or narrowing of the aorta such as Grishman and co-workers³ discovered in their patients.

The final abnormality to be explained was the hypertension in the right arm. This was definite and had been present for some time. This conclusion was supported, first, by the examination of the fundus which disclosed slight indentation of the veins by the arteries where they crossed, and second, by the slightly

*Through the kindness of Dr. Marcy Sussman, the roentgenologist of the Mount Sinai Hospital, New York, N. Y., the angiocardiographic studies were made at that institution (Figs. 5, 6 and 7) and the films interpreted by him.

enlarged left ventricle and the displaced interventricular septum which had been forced to the right (Fig. 5).

The hypertension could be present in this patient as a coincidence, just as it is found not infrequently in so many other young men in the Armed Forces. A more plausible explanation is that the hypertension was associated with the coarctation of the left subclavian artery. In the three cases of localized coarctation of the left subclavian, described by Grishman and co-workers,³ a hypertension in the right brachial artery was found in two patients.



Fig. 7.—Angiocardiogram shows the diodrast in the aorta. White shadows are present where the right innominate and left common carotid arteries normally arise, but there is no evidence of a left subclavian artery.

COMMENT

Unequal radial pulses have been noted in coarctation of the aorta.^{1,4} King⁴, Table IV, cited nine case reports gathered from the literature in which the blood pressure in the right arm was definitely higher than that in the left. These patients may have possessed a coarctation of the left subclavian artery, but the aorta proper was narrowed since the blood pressure of the legs was lower than that of the arms. This is the discrepancy in blood pressure of the upper and lower extremities found in the ordinary case of coarctation of the aorta.

Grishman and associates³ were the first to make a diagnosis of the atypical coarctation of the aorta with absence of left radial pulse by means of the diodrast method. Our case differs from theirs in that our patient revealed no extensive involvement of the aorta at the level of the isthmus and distal to the arch; the left radial pulse was not absent but was diminished in our patient; and, finally, a right-sided aorta was present.

Grishman and co-workers suggested that the diagnosis of atypical coarctation of the aorta may be suspected on clinical and polygraphic examinations but can be proved only by angiocardiographic study. We think that one should go further. We predict that a small or absent left radial pulse, with a hypertension in the right arm, but with the normal expected arterial tension in the femoral vessels, will often disclose a localized coarctation of the left subclavian artery. On the basis of the report by Grishman and co-workers, we suspected this diagnosis in our patient before the diodrast solution was used for confirmation.

When the left radial pulse is small or obliterated, other common conditions should first be thought of and eliminated before the diagnosis of coarctation of the left subclavian artery is hazarded. A large cervical rib is not uncommon. Many normal people can shrug their shoulders back and up and temporarily decrease, or totally obliterate, the radial pulse. Of course, in our patient the pulsation was permanently affected. A congenital anatomic variation in the course of the radial artery, an aortic aneurysm, or a tumor compressing the subclavian artery is to be considered before a diagnosis of coarctation of the left subclavian artery is made.

Hypertension is almost invariably present in typical coarctation of the aorta.^{1,2} Steele³ believes that not only is a systolic hypertension of the upper extremities present, but he maintains that the diastolic arterial tension in the lower extremities (and "inferentially the peripheral resistance") is often increased. He is of the opinion, therefore, that the hypertension in the typical coarctation of the aorta is a compensating mechanism to increase the general vascular tone in the whole body, lower extremities as well as upper. In our patient, then, the hypertension would simply be associated, perhaps reflexly, with the localized atresia of the left subclavian artery. It would be a systemic response of the arterioles to constriction of a large branch of the aorta.

The nerves in the carotid sinus and the arch of the aorta play an important role in controlling blood pressure. In a congenital malformation involving the aorta at the mouth of the subclavian, it is not illogical to expect an effect on arterial tension in the body, and seemingly this is always an elevation. The decrease in tension in the left arm was due to mechanical constriction of the left subclavian artery.

The bradycardia (heart rate, 42 beats per minute) may have been the slow pulse so often met with in athletes or it may have been produced by the nerve mechanism in the aorta in a way similar to that by which the hypertension was produced.

The absence of symptoms in this patient with both a right-sided aorta and a coarctation of the left subclavian artery is not surprising. The former congenital malformation is often discovered by accident. Lewis² studied the typical type of coarctation of the aorta in English Army veterans of World War I. He found that many had performed hard physical work for many years with no symptoms. In coarctation limited to the left subclavian artery, the arm undoubtedly receives a sufficient blood supply from collateral sources.

SUMMARY

A case has been described of right-sided aorta with coarctation of the left subclavian artery. The diagnosis was made clinically and by ordinary x-ray film and then confirmed by angiocardiographic films.

A small or absent left radial pulse in the presence of a hypertension in the right arm and a normal expected blood pressure in the lower extremities should lead to the consideration of the diagnosis of a localized coarctation of the left subclavian artery. Such causes as cervical rib, anomalous course of the left radial artery, tumors, and aortic aneurysm must first be investigated.

With a localized coarctation of the left subclavian artery, just as with the typical coarctation of the aorta, a hypertension is usually present. It is probably a reflex mechanism originating from the nerves in the aortic arch and producing an increased vascular tone in all the extremities.

Localized coarctation of the left subclavian artery frequently is discovered by accident. The patient presents no anatomic or physiologic defect in the left upper extremity except the small or absent left radial pulse. Hard work is quite compatible with the lesion.

REFERENCES

1. Abbott, Maude E.: Coarctation of the Aorta of the Adult Type. A Statistical Study and Historical Retrospect of 200 Recorded Cases, With Autopsy of Stenosis or Obliteration of the Descending Arch in Subjects Above the Age of Two Years, *AM. HEART J.* 3: 381, 574, 1928.
2. Lewis, T.: Material Relating to Coarctation of the Aorta of the Adult Type, *Heart* 16: 205, 1933.
3. Grishman, A., Sussman, M. L., and Steinberg, M. F.: Atypical Coarctation of the Aorta, With Absence of the Left Radial Pulse, *AM. HEART J.* 27: 217, 1944.
4. King, J. F.: The Blood Pressure in Stenosis at the Isthmus (Coarctation) of the Aorta; Case Reports, *Ann. Int. Med.* 10: 1802, 1937.
5. Steele, J. M.: Evidence for General Distribution of Peripheral Resistance in Coarctation of the Aorta. Report of Three Cases, *J. Clin. Investigation* 20: 473, 1941.

PAIN OF UNUSUAL DURATION DUE TO PROGRESSIVE CORONARY OCCLUSION WITH ASSOCIATED MEDIASTINAL TUMOR

MAURICE A. DONOVAN, M.D.
SCHENECTADY, N. Y.

ANGINA pectoris due to myocardial ischemia has been thoroughly studied by Keefer and Resnik.¹ They reviewed the former theories regarding this symptom complex and concluded that the coronary circulation became inadequate to meet various demands of the heart muscle when increased above its basal level. Lately, I have attended a patient who had steady, continuous, severe chest pain for eight days. He was unable to sit or lie down during this period. In either position, pain of an agonizing, tearing nature developed. Even while he was standing, some pain was present, but this was controlled somewhat by forty to sixty 1/100 gr. nitroglycerine tablets in the twenty-four hour period. The problem was complicated further by an unexplained tumor mass in the mediastinum between the posterior surface of the heart and the dorsal spine. This case is reported in detail because of the problem in diagnosis, the unusual fact that the patient was compelled by his pain to remain in the standing position continuously for eight days, and finally because of the finding at autopsy.

CASE REPORT

The patient was a 45-year-old man, whose weight was 200 pounds, height 5 feet 11½ inches; he had always been well up to twenty-two months prior to this illness. Previously the patient had been able to walk several miles with ease and had enjoyed hunting and fishing trips. The family history was negative: his father is alive and well at the age of 72; two older brothers have no history of heart disease; and his mother died of a cerebral accident at the age of 52.

The present illness began one year and ten months prior to death. At that time the patient was employed at heavy labor, lifting considerable weight during an eight-hour day. Gradually he noted the onset of substernal distress when lifting. During the course of the next few weeks a sense of pressure was present in the chest after a walk of three blocks at an average rate. He had a complete physical examination at this time, including gastrointestinal x-rays and an electrocardiogram. All studies were negative except the electrocardiogram, which showed low voltage T waves throughout with a definite cove T in the fourth lead (Fig. 1, A). He was advised that some myocardial damage was present, presumably on the basis of coronary sclerosis, given nitroglycerine for acute attacks of pain, and advised to keep his activities within the limits of the myocardial reserve. He gave up heavy work and secured employment of a light, sedentary nature. However, pain on walking continued, but this was promptly relieved by either rest or nitroglycerine. He continued in this state until early January, 1945, at which time he was referred to me for further study.

The essential findings at this time were a clear-cut history of angina on effort, an entirely negative physical examination except for a blood pressure reading of 174/110, a negative Wassermann, and an essentially normal electrocardiogram (Fig. 1, B). A comparison of this tracing with the one taken formerly (Fig. 1, A) shows improved voltage in the QRS complexes and all T waves. There are minor variations present, including more pronounced slurring of QRS₂ and some RS-T

From the Department of Cardiology, Ellis Hospital
Received for publication Jan. 25, 1946

segment changes in Lead IV F, but it was felt that minor deviations of this sort in a single tracing did not justify a definite diagnosis.² A repeated tracing (Fig. 1, C) was made immediately after the patient had exercised by the two-step method of Master.³ This suggested temporary myocardial ischemia since it showed a depression of more than 0.5 mm. in the RS-T segment in Lead I and Lead IV F. The blood pressure and pulse rate had returned to their original levels within two minutes. After the last tracing was studied, the previous opinion of coronary artery disease was confirmed, similar advice offered, and enteric-coated aminophylline, 3 gr. four times a day was ordered. The patient returned to his attending physician and was not seen again until five months later, thirty hours prior to death.

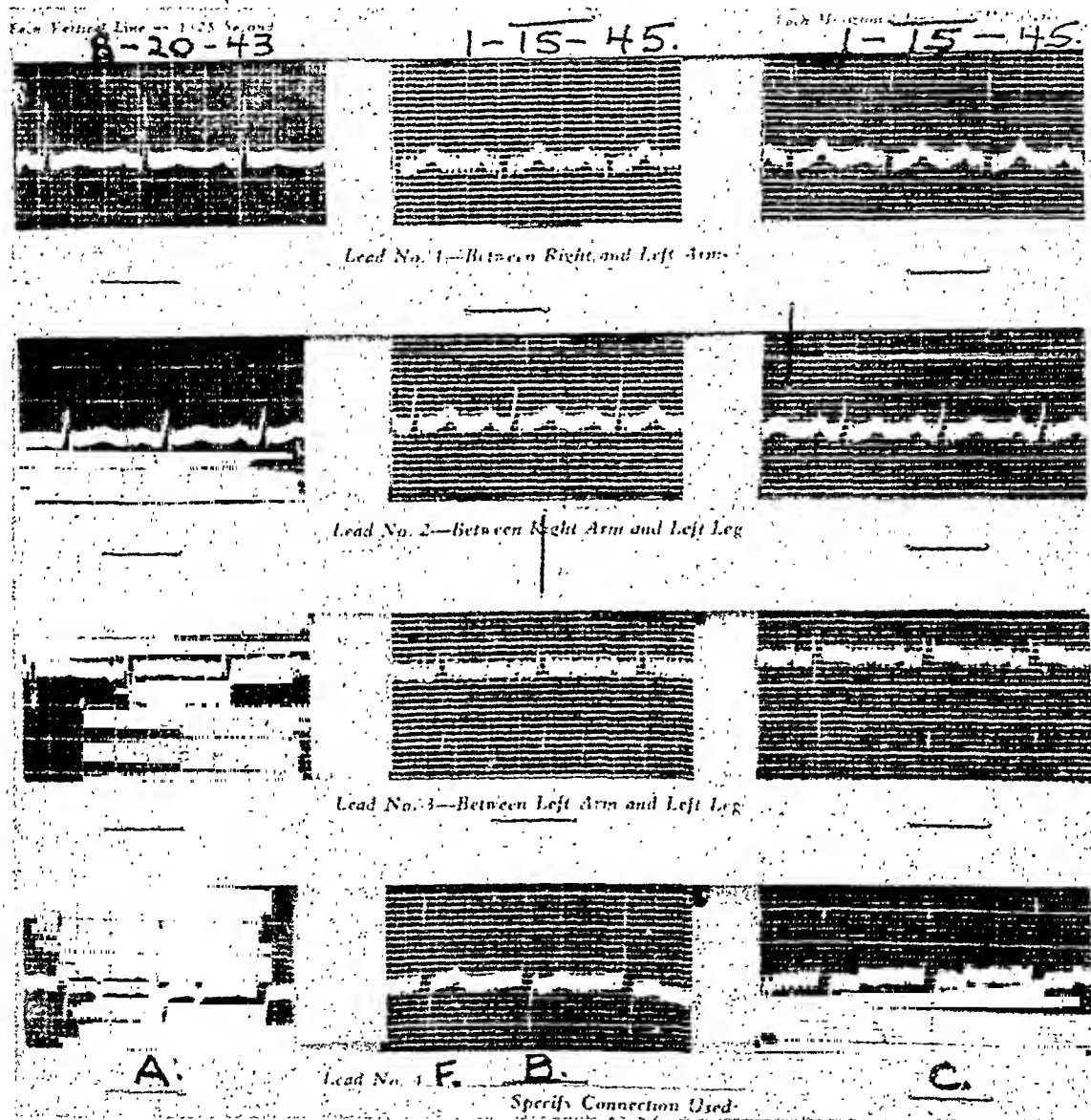
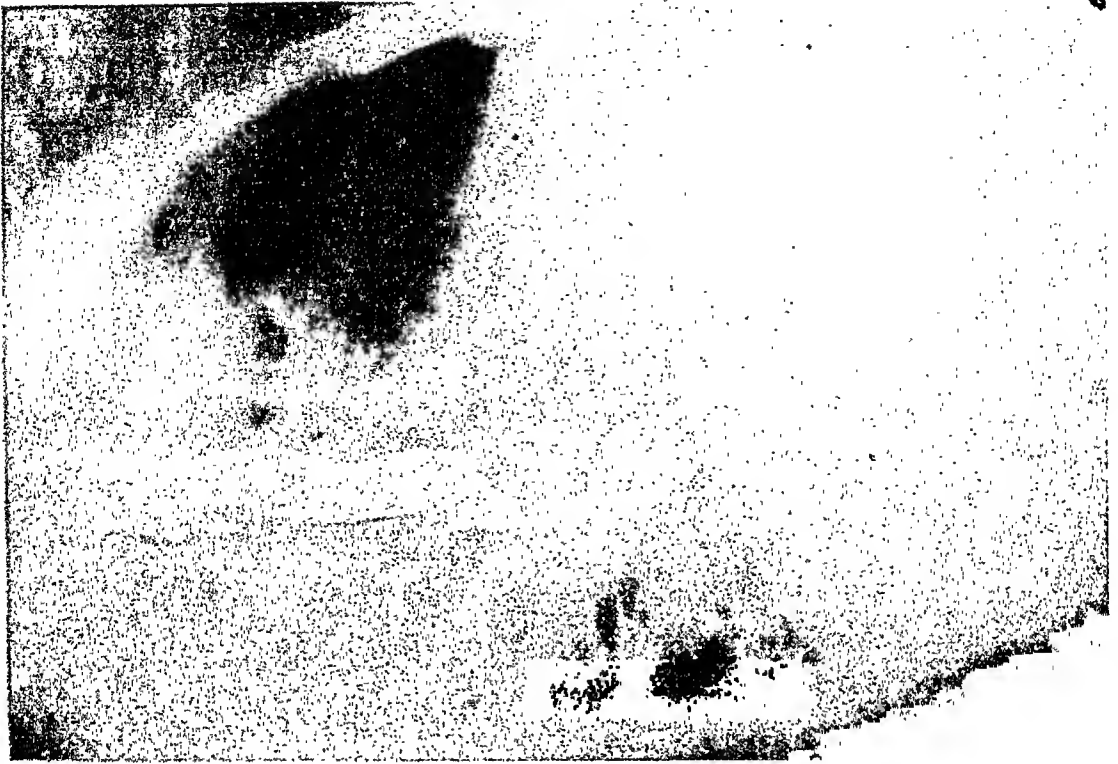
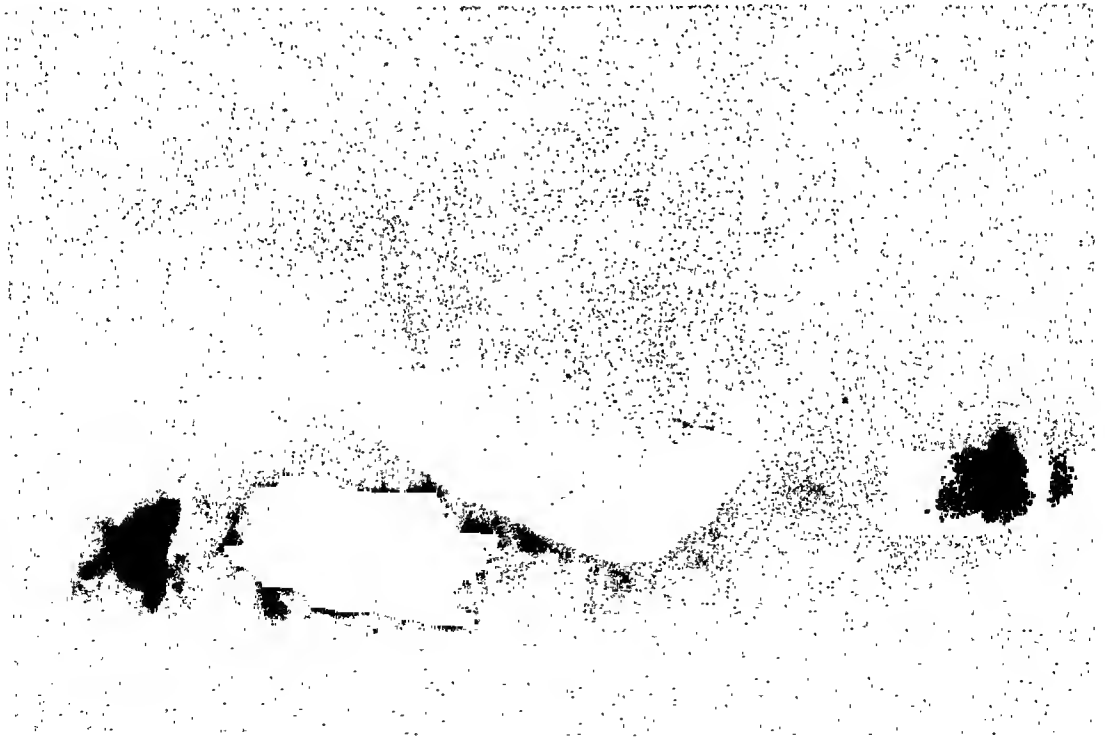


Fig. 1.—Electrocardiograms suggesting myocardial changes.

At this time the history obtained was that for the preceding week the patient had been unable to remain in any but a standing position. Liberal injections of morphine and atropine and papaverine by mouth as well as injection were of little help in controlling the pain. The only procedure of value was to allow the patient to stand upright and take from forty to sixty 1/100 gr. tablets of nitroglycerine during a twenty-four hour period. Although previous studies suggested that coronary insufficiency was present, it appeared questionable that this was the entire problem. Accordingly, the patient was hospitalized. Complete fluoroscopic and x-ray studies of the heart, mediastinum, lungs, esophagus, and great vessels were made. Two of these roentgenograms are



B.



A.

Fig. 2.—Roentgenograms of barium-filled esophagus showing tumor mass of uncertain etiology.

reproduced (Fig. 2). The report and conclusions of the roentgenologist* were as follows: Examination of the chest showed a symmetrical bony cage. The cardiac shadow generally was within the limits of normal in size, but there was a tumor mass projecting from the posterior surface of the heart, deflecting the esophagus posteriorly and to the right and producing a large central filling defect with no particular obstruction. The mass might have originated in the wall of the esophagus, but was not associated with the mucous lining. Impression: Mediastinal tumor or cardiac aneurysm.



Fig. 3.—Photograph showing tumor mass in the esophagus.

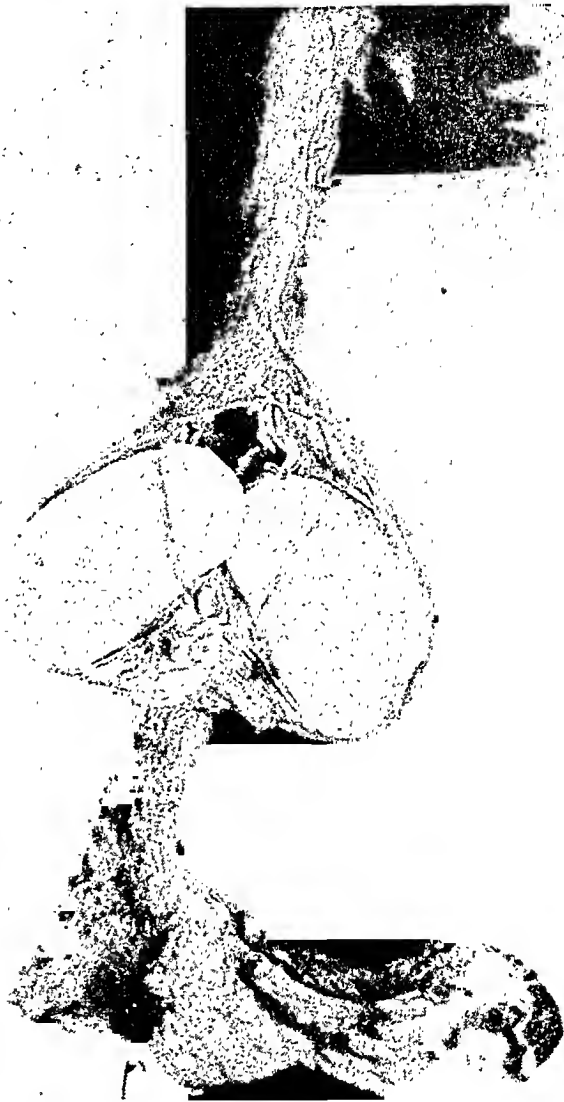


Fig. 4.—Photograph showing esophagus opened and split tumor mass in situ.

At the conclusion of the first and only possible series of x-rays, a careful esophagoscopy was considered for the following day. Meantime the patient secured enough relief from Demerol, 100 mg. intramuscularly every three hours, coupled with occasional injections of morphine $\frac{1}{4}$ gr., to permit him to sit in a chair for several hours and to obtain some degree of relaxation. There were no changes in the general physical examination except that the formerly elevated blood pressure was now 122/100. At no time during the illness was any digestive disturbance present. Unfortunately, due to technical difficulties, it was impossible to secure an electrocardiogram at this time. The patient was much more comfortable until ten minutes prior to death. He

*Dr. K. L. Mitton.

awakened suddenly and stood up, crying out with unendurable chest distress. The nurse left to get another hypodermic, but when she returned the patient had fallen to the floor and was dead.

Post-Mortem Examination.—Autopsy was performed twelve hours after death.* The essential gross findings reported were as follows: (1) Peritoneal cavity: The diaphragmatic domes were in the third and fourth interspace on the right and left sides, respectively. The high position of the domes was apparently caused by the greatly enlarged liver. The serosal surfaces were

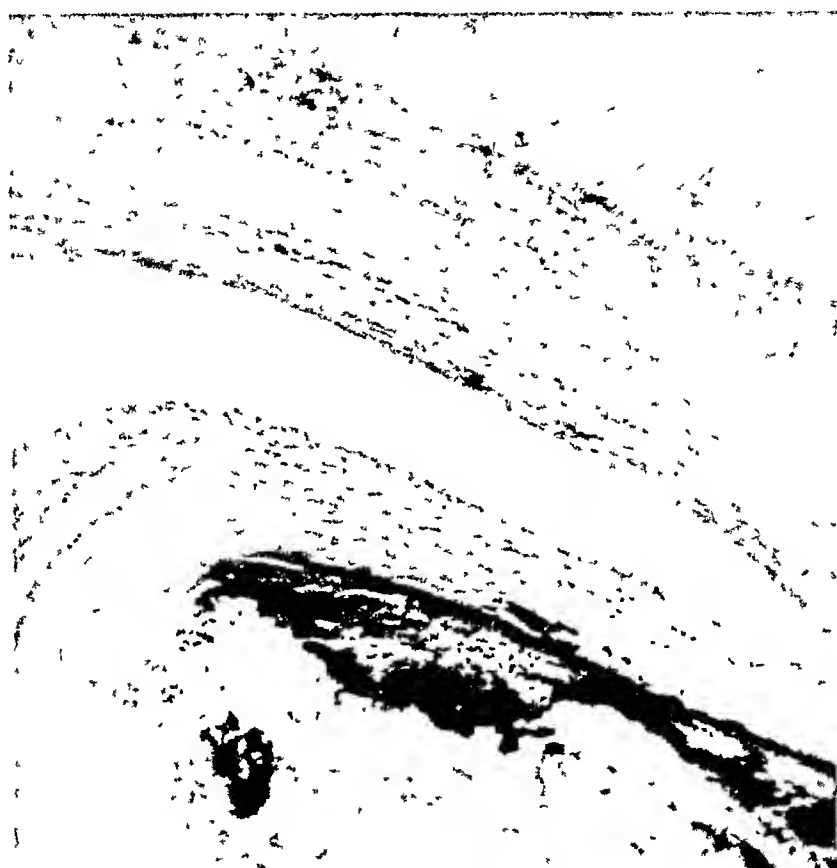


Fig. 5. Photomicrograph ($\times 60$) of large coronary artery showing organized, calcified thrombus.

smooth and shiny. (2) Heart: The pericardial cavity contained about 50 c.c. of straw-colored fluid. The heart weighed 490 grams. The epicardial fat was increased. The cavities were not dilated. The valves showed no lesions. The right ventricular wall was 4 mm. thick and flabby. The left ventricular wall was well contracted and had a diameter of 1.8 centimeters. Small foci of fibrosis were present in the interventricular septum. Both coronary arteries were tortuous

*Dr. M. Hirschfeldt Field, Pathologist.

and rigid. On cross section the walls were calcified and the lumen of the left descending coronary artery was of pin-point size 3 cm. from its origin. The right coronary was also calcified and the lumen was entirely obliterated 2 cm. from its origin. The smaller branches of the coronary arteries were patent. The ascending aorta, the arch, and the descending aorta showed a few elevated plaques in the intima but no calcification. (3) Mediastinum: A firm, oval tumor mass (Figs. 3 and 4) was palpated in the posterior mediastinum. On dissection it was found to arise in the wall of the esophagus. The tumor was well circumscribed 6 by 4.5 by 4 cm. and located

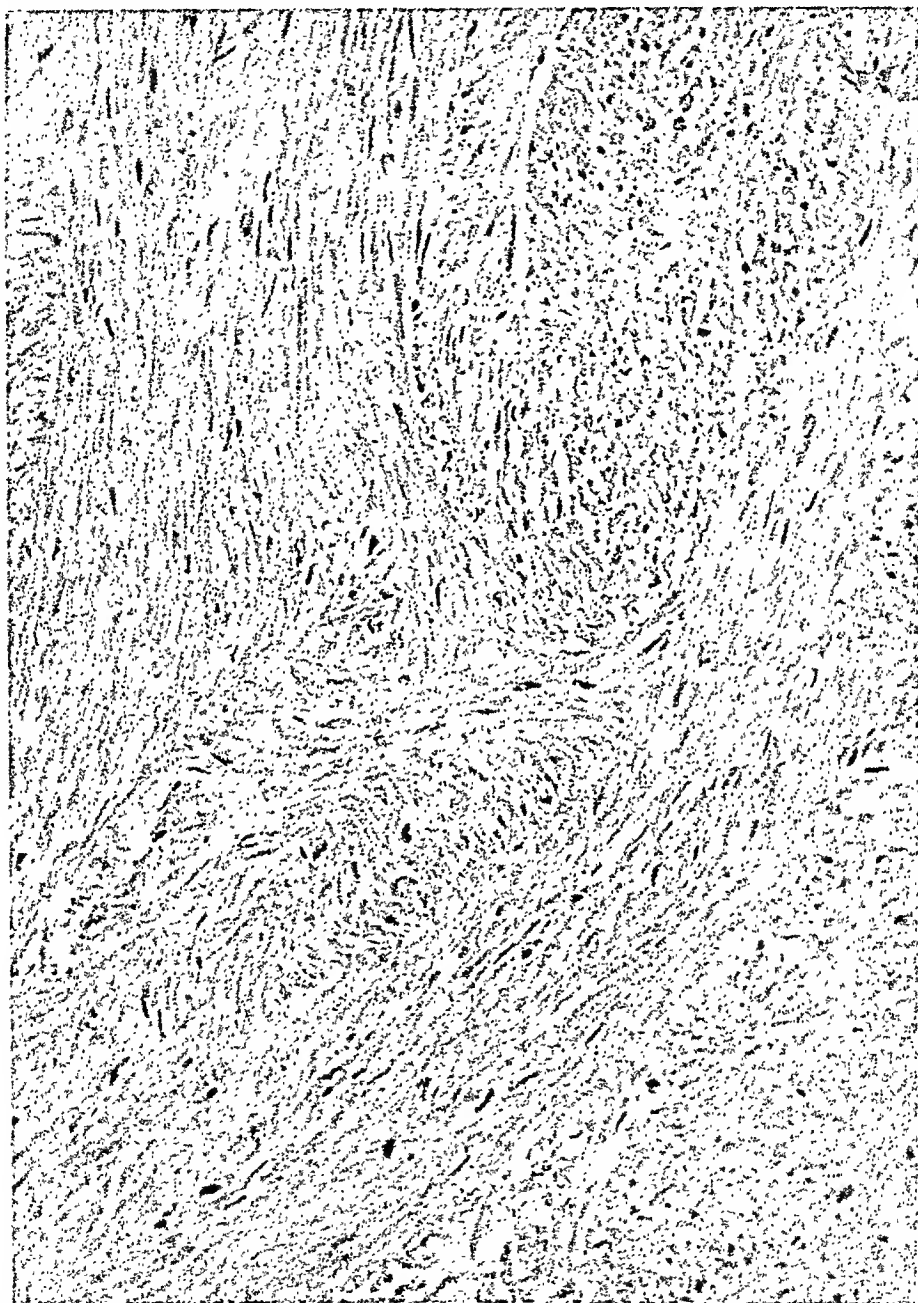


Fig. 6.—Photomicrograph ($\times 240$) of the esophageal tumor showing leiomyoma of the esophagus.

5 cm. above the cardia. The lumen of the esophagus above the tumor showed no distention and there were no gross changes in the mucosa. The cut surface of the tumor was composed of grayish-white trabeculated tissue closely resembling leiomyoma. (4) Liver: The organ was markedly enlarged and weighed 2,700 grams. The left lobe extended to the left midclavicular line. The capsule was smooth. On section, the cut surface was brownish red, smooth, and resilient. The gall bladder and the bile ducts appeared normal. (5) Anatomical diagnoses: coronary sclerosis with complete occlusion of the right coronary artery and partial occlusion of the left descending artery; tumor of the esophagus; enlargement of the liver.

The essential microscopic findings reported were as follows: (1) Heart: Patchy areas were seen in which the muscle fibers were replaced by fibrous tissue. The nuclei in the muscle cell adjacent to these areas were enlarged and square. A large coronary vessel (Fig. 5) showed extensive calcification of the internal intimal layer and proliferation of the external intimal layer to such a degree that the lumen of the vessel was entirely obliterated. The adventitia showed no cellular infiltration. The changes in the aorta were minimal. There was some splitting of the muscle fibers and fat droplets were found in the cells. (2) Esophagus: Sections taken through the tumor (Fig. 6) showed the stratified squamous epithelium, the submucosa, and the nonstriated muscle layer to be normal. (3) Microscopic diagnoses: leiomyoma of the esophagus; fibrosis of myocardium; chronic passive congestion of liver.

DISCUSSION

The main point of the presentation meriting further discussion was the unexpected finding of a benign tumor of the esophagus associated with clinical coronary insufficiency. There was nothing in the history or physical examination to indicate any esophageal disease. The x-ray studies suggested a further possibility that a cardiac aneurysm rather than an esophageal tumor might be present. Although severe chest pain is seen frequently with myocardial infarction, its continuous presence for an eight-day period is most unusual. Occasionally, angina of rest or angina decubitis occurs, but even in these cases there are periods in which pain is absent or when active treatment will terminate this pain for a considerable period of time. It was the unusual presenting complaint of the terminal illness coupled with the unexpected finding of a mediastinal tumor that occasioned some doubt regarding the otherwise clear-cut diagnosis of progressive coronary insufficiency.

In a recent publication by Harper and Tisceno,⁴ a review of the cases of benign tumor of the esophagus that have appeared in the radiologic literature was noted. They list fourteen, to which they add two cases of their own. Among the clinical symptoms summarized by them, one in particular may have some importance in conjunction with the case described here; namely, "Intermittent retrosternal sensation of dull pain or of pressure or of an 'aching sensation' which were usually referred to the lower or middle part of the sternum, being sometimes aggravated by lying on the back." Whether the tumor present in this case was a factor which prevented the patient from either sitting or lying down is open only to speculation. It has been found⁵ that the general blood flow is greater in the recumbent position and thus the heart has more work to do than with the patient sitting or standing upright. It is possible in this instance that the myocardial reserve was so exhausted that standing may have been more economical from the standpoint of heart efficiency. Vinson,⁶ in his monograph on *The Diagnosis and Treatment of Diseases of the Esophagus*, states: "Although benign tumors are not observed often, they occur frequently enough to require consideration in patients who present unusual symptoms referable to the esophagus. Myoma, which is the most common benign tumor of the esophagus, does not produce symptoms unless it attains considerable size. Diagnosis can rarely be made during life, but at many post-mortem examinations tumors of this type are noted." In a consideration of the diagnosis of this condition he

further states: "Roentgenoscopic study frequently reveals defects in the lumen of the esophagus, which may suggest the presence of a large tumor that does not cause obstruction to passage of a radio-opaque meal into the stomach. When such defects are noted, benign tumor should be suspected. In many cases diagnosis cannot be made without removal and microscopic study of the tumor during life or at post-mortem examination."

Thus it may be concluded that tumors of this type are not common and often cause no symptoms nor signs during the life of the patient. On the basis of these facts it is most likely that the clinical picture presented was due entirely to myocardial ischemia resulting from progressive coronary artery disease.

SUMMARY

This case is presented because of the unusual duration of chest pain, the fact that the patient had to stand upright for a continuous eight-day period, the extreme degree of coronary sclerosis with only suggestive electrocardiographic changes, as well as the difficulty added to the diagnostic problem by the presence of a mediastinal tumor of uncertain etiology. This is offered as a clear instance in which the importance of the history, when carefully taken and properly interpreted, is the deciding factor in the diagnosis of angina pectoris.

It is a pleasure to acknowledge the courtesy shown by Dr. Ellis Kellert, Ellis Hospital, in preparing pictures and photomicrographs of the tumor, as well as the kindness of Dr. H. Dunham Hunt, Saratoga Springs, N. Y., in furnishing the electrocardiogram reproduced in Fig. 1, A.

REFERENCES

1. Keefer, C. S., and Resnik, W. H.: Angina Pectoris; A Syndrome Caused by Anoxemia of the Myocardium, *Arch. Int. Med.* 41: 769, 1928.
2. Graybiel, A., McFarland, R. A., Gates, D. C., and Webster, F. A.: Analysis of the Electrocardiograms Obtained From 1,000 Young Healthy Aviators, *AM. HEART J.* 27: 524, 1944.
3. Master, A. M., in collaboration with Nuzie, H. C., Brown, R. C., and Parker, R. C. Jr.: The Electrocardiogram and the "Two Step" Exercise. A Test of Cardiac Function and Coronary Insufficiency, *Am. J. M. Sc.* 207: 435, 1944.
4. Harper, R. A. K., and Tisceno, E.: Benign Tumor of the Oesophagus and Its Differential Diagnosis, *Brit. J. Radiol.* 18: 99, 1945.
5. White, P. D.: Heart Disease, ed. 2, New York, 1937, The Macmillan Co., p. 594.
6. Vinson, P. P.: The Diagnosis and Treatment of Diseases of the Esophagus, Springfield, 1940, Charles C. Thomas, pp. 153, 155-157.

COMPLETE AURICULOVENTRICULAR BLOCK AND BUNDLE BRANCH BLOCK WITH INTERCURRENT AURICULAR FLUTTER

REPORT OF A CASE

JOSE PROENCA PINTO DE MOURA, M.D.
CAMPINAS, BRAZIL

THE association of auricular flutter with complete A-V heart block was first demonstrated with electrocardiographic proof by Jolly and Ritchie in 1910¹ and is very uncommon. DiGregorio and Crawford² found only two instances in a series of 20,000 electrocardiograms. Willius³ reported only one instance among 40,000 electrocardiograms. Up to 1939, only thirty-one cases had been reported in the literature and since then, additional reports have not increased the total beyond forty cases.

Among the reported cases of auricular flutter with complete A-V heart block, syphilis has been considered the most common etiologic factor, with rheumatic fever next in frequency; hyperthyroidism and congenital anomalies have been thought responsible for a small number of cases. Coronary sclerosis, however, should also receive etiologic consideration since a large proportion of the patients were over 50 years of age. Jourdonais and Mosenthal⁴ have suggested a division of the cases into two types: (1) Patients who have both disturbances consistently and (2) patients who have one arrhythmia consistently and the other as a transient occurrence due to drug administration. Since it is frequently impossible to determine whether or not drug action is concerned, this classification seems rather unnecessary.

CASE REPORT

F. L. S., a 25-year-old man, was admitted to the Cardiological Service of the Irmãos Penteadó Hospital on March 11, 1943, because of dyspnea on effort and at rest and edema of the face, abdomen, and legs. These symptoms had developed suddenly following ingestion of a vermifuge in January, 1943. From the first appearance of the symptoms, heart failure progressed gradually but steadily. Except for long-standing colitis, the patient had considered himself in good health prior to his present illness. His past medical history included epistaxis and "rheumatism" (apparently rheumatic fever) in childhood. He had several episodes of dysentery and frequent upper respiratory infections including pneumonia in 1941, at which date the sputum was negative for acid-fast bacilli. He had used alcohol moderately and had been active in sports, especially football. The family history was irrelevant.

Physical examination on admission to the hospital revealed a man of tall, slender build who was pale and orthopneic. The face, abdomen, and lower extremities were very edematous. The tonsils were hypertrophic. The teeth were carious. The thyroid gland was bilaterally enlarged. There were rales at both lung bases. The heart was greatly enlarged. The rhythm was irregular

From the Instituto de Doenças do Coração Dr. Pinto de Moura.
Received for publication Oct. 13, 1945

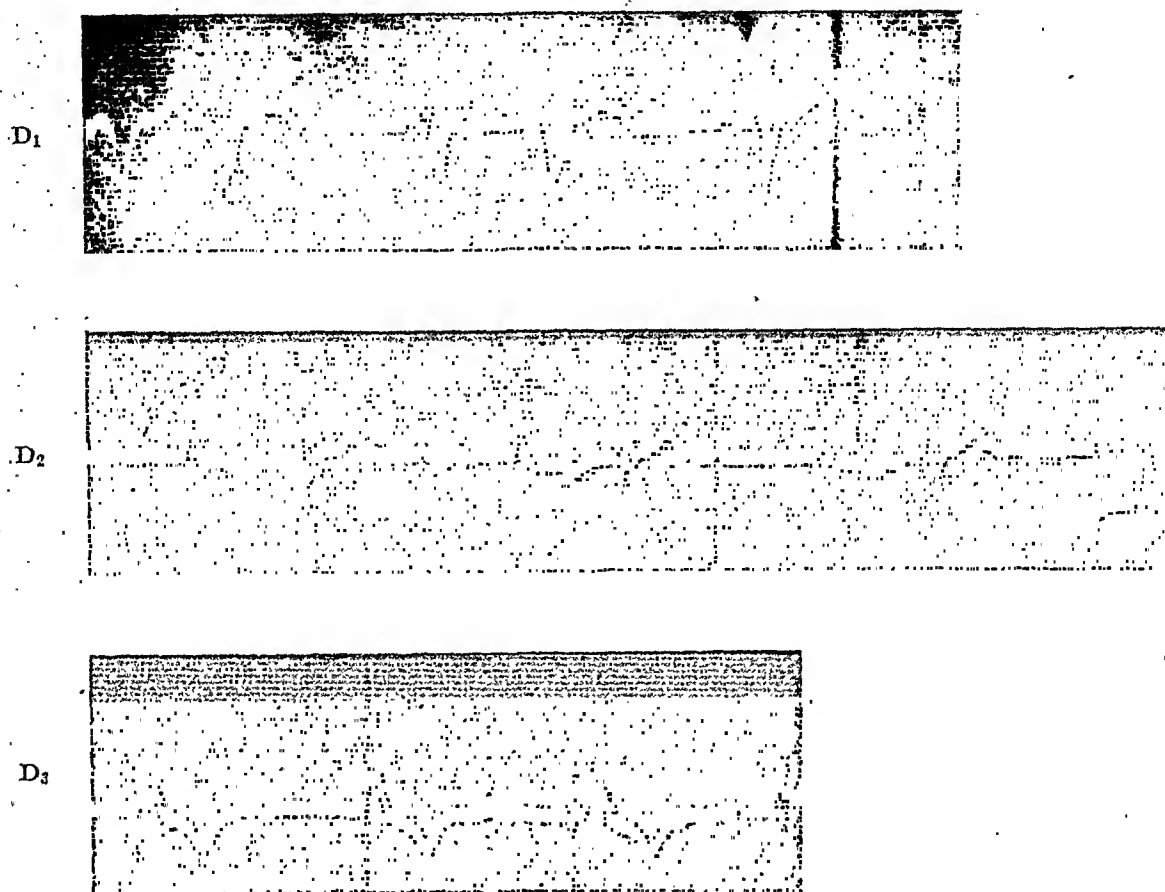


Fig. 1.—Electrocardiogram taken March 12, 1943, following admission to the hospital. Complete A-V heart block and right bundle branch block with ventricular extrasystoles.

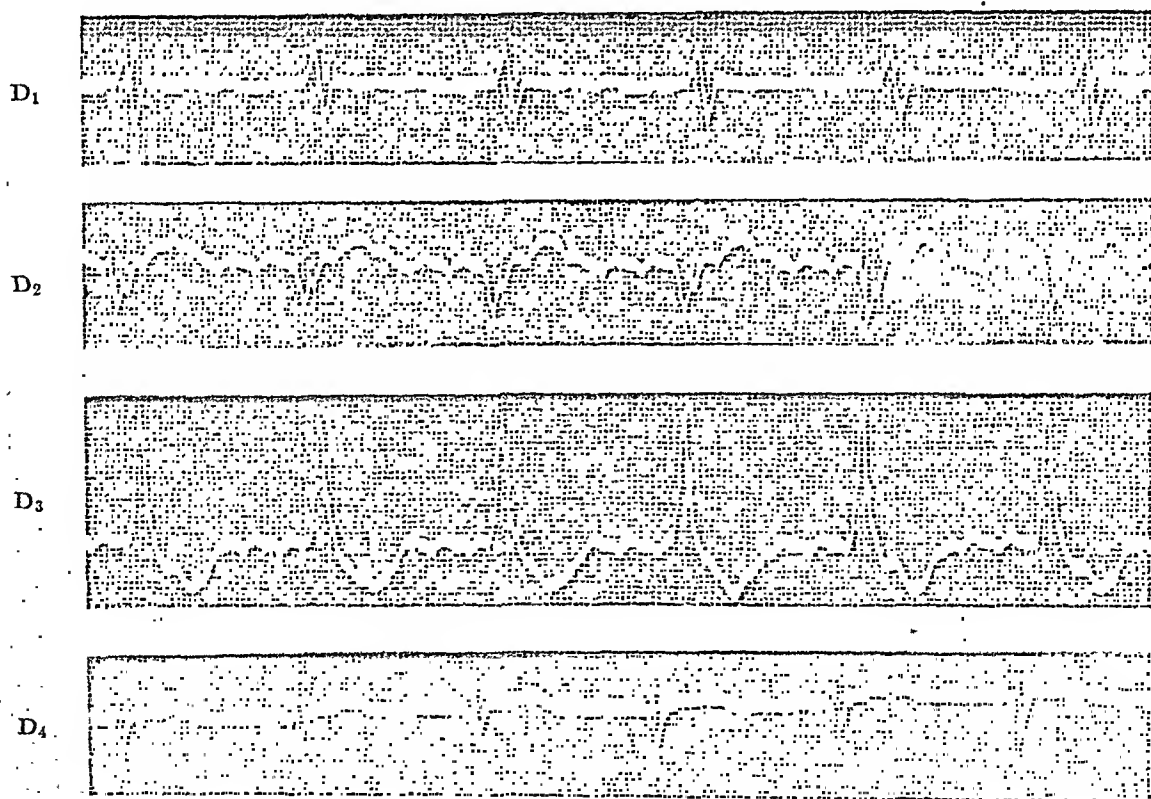


Fig. 2.—Electrocardiogram taken Aug. 4, 1944. Complete A-V heart block persists but auricular flutter has developed. The dominant ventricular complexes are now those which previously represented ventricular extrasystoles.

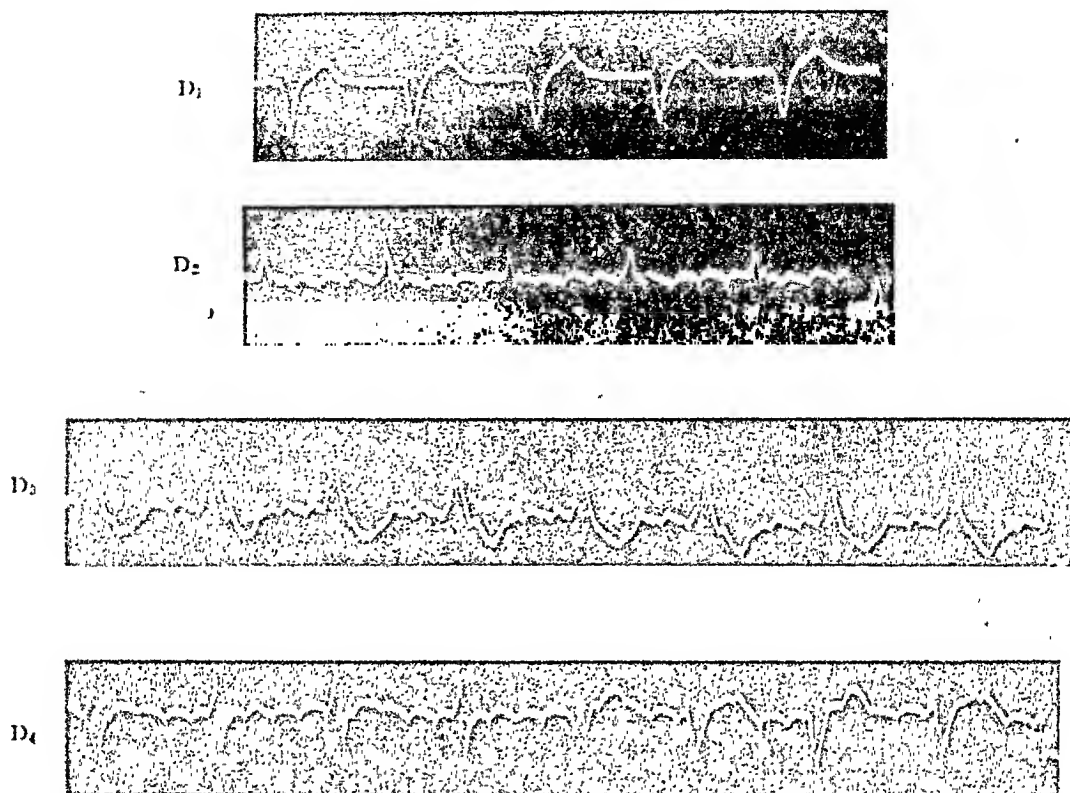


Fig. 3.—Electrocardiogram taken Aug. 5, 1944, following administration of digitalis. Complete A-V heart block and auricular flutter are present as on the preceding day (Fig. 2), but the dominant ventricular complexes are again those which were initially recorded (Fig. 1).

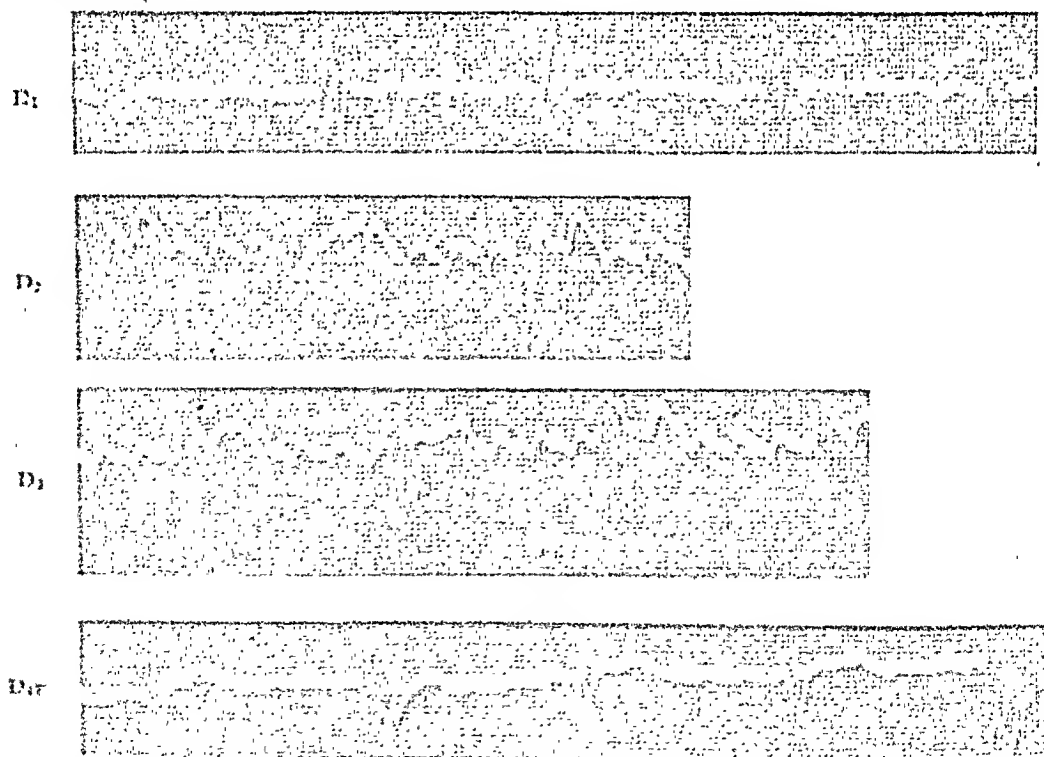


Fig. 4.—Electrocardiogram taken Sept. 27, 1944. Complete A-V heart block and auricular flutter persists, but the dominant beats have reverted to the type which were initially extrasystoles.

with a rate of 48 per minute. The heart sounds were diminished and a loud systolic murmur was audible over the entire precordium. Arterial pressure was 120/50. The liver was enlarged.

Routine laboratory studies showed a negative blood Wassermann reaction. The blood count was normal. Urinalysis was negative except for slight albuminuria. A phonocardiogram recorded a systolic murmur. An x-ray film of the chest revealed a greatly enlarged cardiac silhouette. The electrocardiogram (Fig. 1) showed complete A-V heart block with right bundle branch block and frequent ventricular extrasystoles.

The diagnosis was heart disease: (A) rheumatic fever, pneumonia (?); (B) cardiac enlargement, mitral insufficiency; (C) complete A-V heart block, right bundle branch block, ventricular extrasystoles, congestive heart failure; (D) Class IV.

The patient was confined to bed and treatment included the administration of Salyrgan and of Deriphyllin in 50 per cent glucose solution intravenously. Improvement followed and the patient was soon able to be out of bed. From time to time he left the hospital without permission and attempted to work but was soon forced to return because of aggravation of his symptoms. In August, 1944, following such an absence, an electrocardiogram was made which showed auricular flutter (Fig. 2). It is noteworthy that the complexes which had previously represented the premature beats now constituted the dominant beats. Digitalis was then administered, following which the electrocardiogram (Fig. 3) showed a reversion of the ventricular complexes to the type which had been dominant prior to the onset of auricular flutter. The next electrocardiogram, made in September, 1944, showed that once again the beats which originally had been ectopic had become the dominant type (Fig. 4). No change was present in the last electrocardiogram made in November, 1944.

In December, 1944, heart failure recurred in severe form and progressed in spite of further treatment with digitalis and salyrgan. Death occurred suddenly. There was no opportunity for terminal observations.

DISCUSSION

As previously mentioned, the association of complete A-V heart block with auricular flutter is extremely rare. The present case is presented because of the exceptional association of four defects: complete A-V heart block, bundle branch block, coupled extrasystoles, and auricular flutter. It appears that the rheumatic process affected the conduction system, cicatrization of which produced first the A-V heart block and then the bundle branch block. The extrasystoles could be explained by the necessity for a pacemaker in the lower center. Drug action was not responsible for these phenomena for quinidine was withheld because of the possibility of producing embolism and digitalis was given only in relatively small dosage. Because of the extent of the organic myocardial damage, treatment could be expected to bring about little more than subjective improvement. Such actually was the case and the progress of the disease continued almost uninterruptedly to its fatal termination.

SUMMARY

A case of complete A-V heart block associated with bundle branch block, ventricular extrasystoles, and auricular flutter is reported. This combination of defects is very rare. The apparent etiologic factor was rheumatic fever which caused an unusual degree of damage to the conduction system. The patient was observed over a period of seventeen months; he died of sudden acute heart failure.

The author wishes to express his appreciation to his assistant, Mrs. Ruth Szyszka, for her valuable assistance.

REFERENCES

1. Jolly, N. A., and Ritchie, W. T.: Auricular Flttr and Fibrillation, *Heart* 2: 177, 1910.
2. DiGregorio, N. J., and Crawford, J. H.: Auricular Flutter and Complete Heart Block, *AM. HEART J.* 17: 114, 1939.
3. Willis, F. A.: Auricular Flutter With Established Complete Heart Block, *AM. HEART J.* 2: 449, 1927.
4. Jourdonais, L. F., and Mosenthal, H. O.: Complete Auriculoventricular Block and Auricular Flutter With Observations of the Effect of Quinidine Sulfate, *AM. HEART J.* 11: 735, 1937.

Abstracts and Reviews

Selected Abstracts

Stein, L., and Wertheimer, E.: Cardiac Metabolism and Rigor in Thyroidectomized Rats. Arch. internat. de pharmacodyn. et de therap. 71:129 (Nov.), 1945.

The fact that cardiac rigor develops more slowly in thyroidectomized than in normal rats prompted an investigation of some of the conditions upon which the course of the cardiac rigor curve depends. The studies were made on rats which had been fed a standard carbohydrate diet. The hearts were removed from the living animals in sixty to ninety seconds, suspended in a Ringer bath, and attached to a kymograph for recording their movement.

It was found that the heart produces a normal rigor curve only when it is isolated while the animal is under deep narcosis. A shock type of rigor curve, brief in duration, occurs when the heart is removed after the rats are rendered unconscious by a blow on the head. Previous treatment with caffeine or strychnine, as well as acute asphyxia or poisoning with KCN, produces a similar result. Fatigue and exhaustion or thyrotoxic influence cause a marked curtailment of the rigor curve. Digitals or cardiazol almost completely nullifies the effect of brain shock, asphyxia, or exhaustion on the rigor curve but do not nullify the influence of the thyrotoxic principle.

The cardiac rigor curve of thyroidectomized rats is essentially different from that of normal rats. It is of greater duration and is not influenced by brain shock, caffeine, strychnine, exhaustion, or digitalis. Acute asphyxia has less influence than it has on the curve of normal rats. Chemical rigor produced by mono-iodoacetate poisoning is essentially the same in thyroidectomized rats as in normal rats. The duration of rhythmic contraction of the thyroidectomized rat heart in Ringer solution is twice that of the normal rat heart.

LAPLACE.

Heymans, C., Casier, H., and Delaunois, A. L.: The Influence of Alcholemia on the Proprioceptive Reflexes for the Regulation of Arterial Pressure. Arch. internat. de pharmacodyn. et de therap. 71:103 (Nov.), 1945.

Intoxication by ethyl or methyl alcohol depresses the central nervous system and favors the occurrence of a state of shock, especially post-traumatic cardiovascular collapse. A further study of the subject was made to determine the effect of alcohol on the aortic and carotid sinus reflexes because these are the mechanisms which regulate and maintain the normal arterial pressure, and their suppression predisposes to cardiovascular collapse.

The experiments were performed on dogs which had been anesthetized with chloralosane and were given artificial respiration. In order to limit the proprioceptive regulation of blood pressure to the carotid sinus reflexes, the cervical vagus-aortic nerves were sectioned. The capacity of the animal to react against circulatory collapse was determined by occluding the two common carotid arteries. When the normal compensatory reactions had been determined, a 25 per cent solution of alcohol in isotonic serum was administered intravenously and the intensity of the vaso-hypertensive reflexes of the carotid sinus was recorded at regular intervals.

The results obtained indicate that: (1) weak doses of ethyl alcohol are capable, in the first phase, of stimulating the vaso-hypertensive reflexes of the proprioceptive arterial pressure regulating mechanism; (2) the proprioceptive reflexes of the carotid sinus may suddenly become completely suppressed when the blood alcohol concentration reaches 0.2 to 0.4 per cent (this depressant action predisposes to cardiovascular collapse); (3) the reflexes concerned in the automatic regulation

of arterial pressure are rapidly restored in proportion to the decline of blood alcohol level; intoxication with methyl alcohol produces a similar but more prolonged effect.

LAPLACE.

Moxin, R., Ohlsen, A. S., and Pedersen, A. M.: Arterial Hypertension—Nephrectomy. *Acta med. Scandinav.* 119:439 (VI), 1944.

A 6-year-old boy with a history of hematuria and pyuria since the age of 18 months and of increasingly severe headaches for two years was found to have a blood pressure of 170/120. There was no function of his right kidney; the left kidney was apparently normal. The eye grounds and the electrocardiogram were normal.

An attempt at right pyelography was followed in six hours by a severe hypertensive encephalopathy, with three hours of convulsions and coma. Two other encephalopathic episodes occurred spontaneously during the ensuing three weeks.

The systolic blood pressure fell to below 100 one hour after right nephrectomy was performed. After thirty-six hours of severe oliguria with the blood urea nitrogen rising to 100 mg. per 100 ml. the boy recovered completely. He was followed for eighteen months, during which period no abnormalities of blood pressure or renal function were detectable.

The right kidney was the seat of severe chronic pyelonephritis with marked thickening of the capsule and atrophy of the renal parenchyma. Microscopically the arterioles were greatly narrowed and showed marked thickening of their intimal and medial coats but no necrosis.

The authors believe their case demonstrates that excellent results may be expected from nephrectomy when hypertension, caused by unilateral renal disease, has not yet resulted in significant damage to the opposite kidney or to the cardiovascular system.

SÄVEN.

Duancie, VI.: On the "Paradoxic" Action of the Sympathetic and the Vagus on the Coronary Arteries. *Ztschr. f. Kreislaufforsch.* 31:99 (No. 3), 1942.

The author cites and believes he has confirmed previous reports in the literature that the media of the coronary arteries contains a much larger proportion of spiral fibers than other arteries. The action of spiral fibers is to shorten the vessel and thus enlarge the lumen, producing effects opposite to that of circular fibers. Likewise, relaxation of spiral fibers results in lengthening of the vessel and in a smaller lumen. A similar situation is said to exist in the bronchial tree of human beings (*Ztschr. f. Kreislaufforsch.* 31:21 (No. 1), 1942). Human coronary arteries have, in addition, a well-developed longitudinal muscle layer which has an action similar to that of the spiral fibers. It is proposed that in all vessels the contraction of arterial and arteriolar muscle coats results from sympathetic stimulation but that the effect of such contraction is opposite in the coronaries, since the lumen is enlarged through shortening of the vessel length. The results of parasympathetic stimulation are opposite. Thus the postulation of a different muscle reaction in coronary vessels (and the human bronchial tree) from that resulting in other arteries in the organism would be unnecessary.

SÄVEN.

Huntington, R. W., Ryan, R. D., Butt, H. R., Griffiths, G. C., Montgomery, H., Solley, R. F., and Leake, W. R.: Studies in Rheumatic Fever: II. Absorption of Salicylates. *Ann. Int. Med.* 21:1029 (June), 1946.

This report deals with observations made among a group of patients with rheumatic fever in whom treatment consisted of large doses of salicylates administered by the oral, rectal, and intravenous routes. The comparisons were made between the administration of sodium salicylate and of acetyl salicylate. This medication was given with and without sodium bicarbonate. On the basis of serum salicylate levels it was concluded that salicylate is readily absorbed from the upper end of the gastrointestinal tract but is poorly absorbed from the lower end. For this reason the authors recommend that salicylate should never be given in enteric-coated tablets or by rectum. They also suggest that the gastric irritation resulting from the administration of the ordinary tablets of sodium salicylate by mouth can be minimized by the simultaneous administration of

food or bicarbonate. In their experience, bicarbonate sufficient for this purpose (60 gr. daily) should not cause a definite reduction in the serum salicylate level. They also found that the concomitant administration of bicarbonate did not reduce the blood level of salicylate below what would ordinarily occur without the bicarbonate. They also stressed the fact that there is practically no need for resorting to intravenous salicylate administration inasmuch as adequate blood levels can be achieved by giving the drug by mouth.

WENDKOS.

Fagin, I. G., and Schwab, E. H.: Spontaneous Mediastinal Emphysema. *Ann. Int. Med.* 24:1052 (June), 1946.

In this article the authors describe three new cases of mediastinal emphysema and review all previously published cases. The differentiation of this condition from true cardiac disease, such as acute myocardial infarction, acute pericarditis, dissecting aortic aneurysm, and pulmonary embolism is stressed. In this regard, the absence of significant electrocardiographic changes as a diagnostic feature of mediastinal emphysema is emphasized. The proper use of the roentgenogram as a diagnostic aid is demonstrated. The frequent association of pneumothorax is also pointed out and its mechanism is briefly discussed. The benign and self-limited nature of spontaneous mediastinal emphysema is reaffirmed. There is an adequate discussion of mediastinal crepitation (Hamman's sign) as a diagnostic feature. Included are reproductions of sound tracings which show how the acoustic qualities of mediastinal crepitation differ from those of a pericardial friction rub.

WENDKOS.

Moberg, G.: Intravascular and Extravascular Pressure in Valsalva's Experiment. *Acta radiol.* 27: 392 (No. 3-4), 1946.

The validity of Westermarck's method of measuring pulmonary artery pressure by holding the breath against a measured pressure which diminishes the size of the pulmonic vascular shadows is questioned. The author believes that this or any modification of the Valsalva experiment would have a selective effect on the pulmonary arterial circulation only if the chest were open and the lung inflated by the intratracheal pressure. The Valsalva experiment is asserted to convert the whole of the abdomen and thorax into a chamber in which there is a relatively uniform increase of pressure which would act on the great vessels and the right ventricle equally with the pulmonary capillaries except for the elastic recoil of the lungs. This results in the blood being forced from the trunk into the extremities, head, and neck. The diminution in size of vascular shadows would thus be due to a smaller amount of blood in vessels of widely varying size and pressure and not to an effect on the pulmonary vascular bed alone and would therefore have no significant relation to the pulmonary arterial pressure.

SAYEN.

Laquime, J., and van Heerswyngheles, J.: A New Classification of Congenital Cardiopathies. *Acta med. Scandinav.* 118: 244 (No. 1-3), 1944.

A classification is suggested based on the presence or absence and the type of vascular shunt between the greater and lesser circulations in congenital heart disease. This would avoid the use of cyanosis as a criterion as was done by Abbott. The difficulties involved in evaluating the multiplicity of factors affecting cyanosis are detailed. The authors suggest cases be grouped as follows:

1. Those with no vascular shunt.
2. Those with a shunt, which may be of two types:

(A) Arteriovenous shunts, evidenced by reduction in carbon dioxide tension in the pulmonary arterial blood which can be measured by rebreathing various mixtures of a gas and obtaining equilibrium. This group would include interventricular and aortic septal defects, patent atrial septum, patent ductus arteriosus, and transposition with septal defect.

(B) Venoarterial shunts, determined by studying arterial unsaturation in the systemic circulation. This group would include the tetralogies of Fallot and Eisenmenger, cor biloculare, and other similar defects.

SAYEN.

Brammer, D.: Proteinuria of Effort and Its Significance in the Diagnosis of Congestive Heart Failure. *Acta med. Scandinav.* 121: 252 (No. 3), 1946.

The author believes that the concept of "physiologic" proteinuria up to 2.0 to 8.0 mg. per cent, which is based on the work of Mörner (1895), is incorrect. The usual clinical tests for albuminuria are relatively inaccurate and are negative unless a proteinuria of at least 5.0 to 10.0 mg. per cent is present. Using precipitation by salicylsulfonic acid and a set of dilute solutions of precipitated serum as comparators, proteinurias of less than 1.0 mg. per cent can be measured. Of 50 "normal" patients, none showed more than 1.0 mg. per cent of protein at rest; exercise (forty knee bends) did not increase this significantly. Twenty-five of thirty patients with acute febrile diseases had 1.4 to 7.1 mg. per cent of proteinuria, whereas only 40 per cent of the group showed a positive albumin test by routine methods. Patients with acute glomerulonephritis or acute pyelonephritis showed increased proteinuria after exercise. Those with chronic renal disease did not.

Nineteen cardiac patients without failure showed no increase above the author's strict normal standards at rest or after exercise. Of thirteen patients with congestive failure, exercise produced significant increases of protein above their normal resting figures in patients with mild signs of congestion. Patients with more severe congestion had abnormal proteinuria at rest and a further considerable increase after exercise. This occurred with left-sided failure and not necessarily only when venous pressure was elevated. There was no quantitative relationship between the amount of proteinuria and the severity of congestive failure. In the absence of acute renal or febrile systemic disease, a resting proteinuria greater than 1.0 mg. per cent and a postexertional proteinuria greater than 2.0 mg. per cent in cardiac patients is felt to be evidence of congestive heart failure.

SÄYEN.

Scherf, D., and Schlachman, M.: The Effect of Methylxanthines on the Prothrombin Time and the Coagulation of the Blood. *Am. J. M. Sc.* 212: 83 (July), 1946.

The investigations reported show that there is a definite shortening of the prothrombin time and of the plasma coagulation time following an intravenous injection of aminophylline. The changes were often found within one hour after the injection, reached a maximum four to five hours later, and often persisted after twenty-four hours. Since the intravenous injection of theophylline with sodium acetate had a similar effect, the action is not bound to the ethylenediamine which is used as a solvent for the theophylline. The oral administration of methylxanthines was likewise found to shorten the prothrombin and plasma coagulation times. The possibility is suggested that the increased coagulability of the blood may augment the danger of venous thrombosis in the bedridden patient or the risk of coronary thrombosis in a patient with coronary sclerosis.

On the other hand, it is suggested that the methylxanthines may be of value as styptic agents in hemorrhagic disease. The cause of the hyperprothrombinemia produced by these drugs is unknown, but a functional stimulation of the hepatic tissue has been suggested as a causative factor.

DURANT.

De Takats, G., Fowler, E. F., Jordan, P., and Risley, T. C.: Sympathectomy in Peripheral Vascular Sclerosis. *J. A. M. A.* 131: 495 (June 8), 1946.

These authors discuss their experiences in using sympathectomy for the treatment of peripheral vascular sclerosis of the lower extremities. The indications for sympathectomy were as follows: patients with popliteal, femoral, or aortic occlusions who showed a favorable response to paravertebral block with procaine and whose visceral vascular involvement was subclinical or slight (no hemiplegia, no coronary occlusion, no advanced nephrosclerosis); patients with or without diabetes whose chief complaint was continuous intractable burning pain associated with osteoporosis, who obtained relief from paravertebral block and who otherwise would require a supra-epidural amputation for causalgic states. The age group between 40 and 50 was found to be most favorable.

The material consisted of twenty-five patients ranging in age from 39 to 66 years who were placed in the vascular sclerotic category because of (1) definite evidence of sclerosis elsewhere; (2) absence of a history of segmental phlebitis or arteritis in earlier years and no involvement of radial arteries; (3) high pulse pressure, hypertension, hypercholesteremia, or hyperglycemia.

The following results were obtained. Group I included nine middle-aged sclerotic patients with a previous walking ability limited to a few blocks. These patients were greatly benefited by lumbar sympathectomy: their walking ability improved, occasionally for unlimited distances; in two patients it improved to a point where they developed angina of effort. Group II was made up of patients whose walking ability ranged from one-half to two blocks. Operation was undertaken mainly to prevent gangrene. Not a single patient developed gangrene on the sympathectomized side; two patients lost their legs on the side not operated upon, which were originally the better legs. Group III included patients requiring amputation or who had already lost one leg by amputation. As a result of lumbar sympathectomy the authors were enabled to do three toe amputations and three lower leg amputations in the presence of a type of circulation which their previous experience indicated would have necessitated a supracondylar amputation. The patients in Group IV had intractable pain, diffuse osteoporosis, and glossy edema. These patients were regarded by the author as belonging to the casalgic state. These patients also showed improvement after sympathectomy.

BELLET.

Leevy, C. M., Strazza, J. A., Jaffin, A. E.: Fluids in Heart Failure. J.A.M.A. 131: 1120 (Aug. 3), 1946.

One hundred twenty-two patients with congestive heart failure were studied to evaluate the relative merits of restriction of fluid intake, allowing fluids ad libitum, and forcing fluids.

Currently, most clinicians allow only 1,000 to 1,500 c.c. of fluids daily as an integral part of their cardiac regimen in treating congestive heart failure. They feel that more may increase the burden on the heart. Members of the ad libitum school feel that limiting or forcing fluids may prove difficult, hazardous, or uncomfortable, whereas champions of the forcing-fluids school of thought believe that with the ever-present renal function impairment in cardiac decompensation, more water than normal is necessary to eliminate normal waste products without having the kidney work at maximum capacity.

All patients admitted to the general medical service with congestive heart failure were divided into three groups: Group I consisted of thirty-six patients on a restricted fluid regimen of 1,200 c.c. daily; Group II was composed of forty-eight patients placed on a fluids ad libitum regimen; Group III included thirty-eight patients who received a minimum daily fluid intake of 3,000 cubic centimeters. All patients were placed upon the same fundamental cardiac regimen, the only essential difference being the amount of fluid intake. Patients were given an acid ash, salt poor diet which provided sufficient calories, proteins, minerals, and vitamins, and at the same time insured a low sodium intake, low salt intake, and an acid ash.

The following results were noted: In the group permitted to drink fluids ad libitum, the average cardiac patient consumed approximately 1,700 c.c. of water daily in the summer and only 1,300 c.c. in the winter. Patients allowed to drink water as they desired were much more comfortable than members of the other groups. In no instance was increased intake associated with evidences of the circulation becoming overburdened, increase of decompensation, or water intoxication.

Of the thirty-eight patients on a forced-fluid regimen with a minimum daily intake of 3,000 c.c., seven (18.3 per cent) became nauseated and were compelled to discontinue the treatment. Of those adhering to forced fluids, twenty-seven felt greatly improved. The average amount of fluid consumed daily by the individuals of this group was 5,750 cubic centimeters. In no instance did pulmonary edema or hypertensive encephalopathy incident to cerebral edema follow the regimen of forced fluids.

Of thirty-six patients in whom fluids were restricted, 27.7 per cent complained of thirst (52.6 per cent of those observed during summer and 47.4 per cent during winter); 13.6 per cent of patients discontinued restriction because of thirst. Restricted fluids may lead to dehydration with disorientation.

These authors conclude that with restricted sodium intake, restriction of water is unnecessary in treating cardiac decompensation—that restriction of fluids increases the discomfort of the patient and may prove deleterious. In most decompensated cardiac patients, forcing fluids will neither retard nor facilitate compensation. The average patient with congestive heart failure should be allowed to drink water as it is desired and should consume enough to maintain a daily minimum urinary output. When congestive heart failure is complicated by sepsis, fluids should be forced to obtain optimum therapeutic results. Likewise, water intake should be increased to prevent dehydration where there is intrinsically impaired renal function or excessive skin or urinary water loss.

BELLET.

Levy, R. L., White, P. D., Stroud, W. D., and Hillman, C. C.: **Overweight: Its Prognostic Significance in Relation to Hypertension and Cardiovascular Renal Disease.** J. A. M. A. 131: 951 (July 20), 1946.

A statistical analysis was made of the medical records of 22,741 officers in the United States Army to determine the prognostic significance of overweight noted in the course of annual physical examinations.

An officer was considered to be overweight when he was heavier, by twenty pounds (nine kilograms) or more, than the standard given in army regulations, calculated according to height and age. By sustained hypertension was meant a reading of over 150 systolic or 90 diastolic persisting throughout one examination and not followed in subsequent examinations by lower levels.

When the combination of overweight, transient hypertension, and transient tachycardia was present, the probability of the later development of sustained hypertension was twelve times as great as in normal controls. In the case of retirement with cardiovascular renal diseases, the probability was four times as great. Overweight alone did not increase significantly the death rate from cardiovascular renal diseases. Transient hypertension or transient tachycardia or overweight by itself increases the probability of the later development of sustained hypertension and of cardiovascular renal disease.

BELLET.

Iandolo, C., and De Rysky, C.: **Clinical Studies on Venous Pressure. 1. Technique: Venous Pressure in Normal Individuals.** Cuore e Circ. 29: 97, 1945.

The authors studied the venous pressure of normal subjects by the direct method. A variation from usual technique was the graphic recording of the venous pressure. Oscillations of the venous pressure due to three possible causes were observed: (a) arterial pulsations (transmitted); (b) respiratory changes; (c) changes of the venous tonus.

The venous pressure tracings varied in different individuals and at times presented ample and frequent oscillations, caused by variations of venous tonus. Values between 20 and 170 mm. water were considered normal by the authors.

LUISADA.

Mallen, M. S., and Pallares, D. S.: **A Study of Chronic Cor Pulmonale.** Arch. Inst. cardiol. México 16: 22, 1946.

Fourteen cases of chronic cor pulmonale were studied from both a clinical and electrocardiographic standpoint. The main symptoms and signs were paroxysmal dyspnea, effort dyspnea, cyanosis, and venous engorgement. Congestive failure was revealed by hepatic enlargement, edema, tachycardia, and prolongation of the arm-to-tongue time. Accentuation of the hilar shadows was present in all cases; enlargement of the pulmonary artery was observed in over 90 per cent of the patients.

The electrocardiographic changes were: P_3 higher than P_1 ; P wave inverted in V_1 but upright in V_2 ; absence of Q_1 ; presence of S_1 and Q_3 ; small R wave in V_2 , V_4 , V_5 , V_6 ; deep S wave in V_4 and V_5 ; T inverted, flat or diphasic in Leads II, III, V_F , V_1 , V_2 , and V_3 .

The above changes were attributed to dilatation and hypertrophy of the right auricle and ventricle.

LUISADA.

Elkin, D. C., and Banner, E. A.: Arteriovenous Aneurysm Following Surgical Operations. J. A. M. A. 131: 1117 (Aug. 3), 1946.

This case was reported because of its rarity. The authors have not encountered a similar instance in the literature. Most of the cases of arteriovenous fistula which have been presented in the literature have arisen as a result of war wounds or from injuries incurred in civilian life. In this report, the authors described a case in which this lesion was produced during a surgical operation, hysterectomy. The most likely explanation of this occurrence is that in transfixing and ligating blood vessels the needle used for this purpose injured the artery and vein at the same time, with the subsequent production of a communication between them.

Following the removal of the arteriovenous fistula, the patient made an uneventful recovery.

BELLET.

Dock, W.: The Predilection of Atherosclerosis for the Coronary Arteries. J. A. M. A. 131: 875 (July 13), 1946.

In this article, Dock makes two points: (1) that arteriosclerotic changes frequently occur earlier in the coronary vessels than in other vessels and (2) that coronary artery disease is more frequent in men than in women, especially before the seventh decade.

From a study of hundreds of soldiers who died of coronary disease, it was apparent that cases of coronary disease without tibial, cerebral, or aortic lesions, which are exceptional after the sixth decade, are the rule in men under 40 years. Coronary thrombosis is not only much more frequent, but also often occurs as a result of a purely local atheromatosis. In those hearts examined at necropsy it was noted that while most of the vessels were relatively free of atheroma, many of them had unusually thick intimal layers at places in the coronaries where no lipid had yet been deposited and where there was no inflammatory reaction.

Although Spalteholz, Gross, and others mention the remarkable thickness of the coronary intima, as compared with that of the radial, tibial, cerebral, or visceral arteries, this observation has been ignored by most pathologists and clinicians. No satisfactory explanation of the increased susceptibility of the coronary arteries to atheroma has been thus far advanced.

Dock was unable to explain the higher incidence of coronary disease in men as compared with women from the level of the blood cholesterol or the height of the arterial pressure. In the examination of hearts of young adults killed in accidents, Dock observed a striking difference in the thickness of the coronary arteries in the two sexes. The men had thicker intimas: coronary arteries of boys no more than 18 years of age often had atheromas in them. In addition, sections were made of the right coronary artery, the left circumflex branch, and left descending branch of twelve infants of each sex who died less than twenty-four hours after birth. He observed in these specimens that the thickness of the coronary intima in male-infants was about three times that in female infants.

He believes, therefore, that the sex differences in coronary disease and, to some extent, the familial differences in incidence seem to rest on an anatomic basis.

BELLET.

Hinton, J. W., and Lord, Jr., J. W.: Analysis of Surgical Failures and Fatalities Following Thoracolumbar Sympathectomy for Essential Hypertension. N. Y. State J. Med. 46: 1714 (Aug.), 1946.

Although thoracolumbar sympathectomy has a definite place in the treatment of essential hypertension, there is no test or series of tests by which we can measure the chance for a successful result. In order to justify such a procedure, the surgeon must offer a much greater life expectancy.

than that anticipated from the medical treatment of hypertension. After the various cardiac and renal function tests have been made, one can usually arrive at an opinion as to whether the patient is a safe surgical risk, but the final outcome following operation is difficult to prognosticate.

Patients in whom the pressure drops the most under sodium amytal seem to offer the highest percentage of good results. With reference to the question of age at the time of operation, the experience of these authors is as follows: in thirty-four cases including both sexes above 50 years of age at the time of operation, they found in six-month to three-year follow-ups that twenty-six, or 76.5 per cent, were improved, only eight, or 23.5 per cent, were unimproved, and that there were no deaths. This compares most favorably with the over-all failure and mortality figure for 152 cases, which was 20.5 per cent.

During the past four years, 227 patients have been operated upon for essential hypertension by these authors. One hundred fifty-two cases were operated upon by the Smithwick technic with follow-ups ranging from six months to three years. The total mortality of this group in and out of the hospital was 18, or 11.8 per cent. There have been thirteen patients, or 8.5 per cent, unimproved. This gives a total of poor results and fatalities of 20.5 per cent to date.

Since June, 1945, these authors have extended the operation to the higher thoracic ganglia and have included the ganglia from the third thoracic to the second lumbar inclusive. The immediate mortality was higher in the more extensive operative procedure. However, the authors hope the follow-ups will show better end results with a lower late or out-of-hospital mortality.

They grade the severity of the disease in the four major organs involved in essential hypertension, the eyes, cerebral vessels, heart, and kidneys, from 1 to 4 plus. If the degree of involvement in all organs exceeds 8 plus, they believe it is questionable whether a thoracolumbar sympathectomy will give any lasting results.

BELLET.

Griffith, J. Q., Jr., Padis, N., and Anthony, E.: Selection of Patients With Arterial Hypertension for Treatment by Repeated Injections of Pitressin. *Am. J. M. Sc.* 212: 31 (July), 1946.

Sixty-three persons with hypertension were selected on the basis of (1) positive bio-assay for antidiuretic hormone in serum; (2) negative bio-assay for gonadotropic hormone in serum at the level of 330 mouse units; (3) normal renal function. It has been previously shown that cases of this type frequently respond to pituitary irradiation with a disappearance of the antidiuretic hormone and definite clinical improvement, the blood pressure often returning to the normal range. In view of the experience of Robinson and Farr with repeated injections of pitressin, it was considered probable that this might produce a result similar to that obtained with irradiation. Various methods of applying this treatment were tried; the one that appeared best was the administration of 1 c.c. of pitressin tannate in oil weekly for three weeks, then monthly for three months, and thereafter continuing the injections at monthly intervals until the bio-assay for antidiuretic hormone became and remained negative. Considering the group as a whole, the blood pressure was significantly lowered and symptoms improved in about one-half the cases.

When the procedure described was used, no reactions except a mild urticaria were observed; severe reactions did occur when aqueous pitressin was employed.

DURANT.

Lesine, E. B., and Sellers, A. L.: Testosterone in Angina Pectoris. *Am. J. M. Sc.* 212: 7 (July), 1946.

Testosterone propionate injected intramuscularly and methyl testosterone administered sublingually were found to have no value in the treatment of angina pectoris. However, testosterone preparations were found to be of definite value in relieving the chest discomfort sometimes associated with the male climacterium or the similar precordial ache of neurocirculatory asthenia occasionally encountered in individuals in the age group commonly subject to angina pectoris. In their field of usefulness, parenteral administration of 25 mg. of testosterone propionate two

to three times weekly was found to be preferable to the rather ineffective administration of methyl testosterone sublingually in doses of 10 to 15 mg. daily.

DURANT.

Griffith, G. C., Phillips, A. W., and Asher, C.: Pneumonitis Occurring in Rheumatic Fever. *Am. J. M. Sc.* 212: 22 (July), 1946.

In a group of 1,046 rheumatic fever patients in a United States Naval Hospital, pneumonitis was found in 119 cases. A study of these cases revealed that pneumonitis is one of the prominent manifestations of active rheumatic fever. It is defined as a manifestation of rheumatic fever characterized by an inflammatory process of the lung and pleura, with an insidious onset, migrating consolidation, and frequent pleurisy with or without effusion. Occurring in approximately 11 per cent of rheumatic fever cases, it is seen in 53.1 per cent of the acute fulminating type, in 27.4 per cent of the polycyclic type, and in 2 per cent of the mild monocyclic type. Depending upon its time of appearance in the rheumatic fever state, three types may be recognized: primary acute, secondary acute, and subclinical. The diagnosis is based entirely on the exclusion of the other types of pneumonia and the concomitant development of other manifestations of acute rheumatic fever. The roentgen ray findings are not specific, but the rapid shift of the areas of density, the rapid development of an effusion, and the close adherence of the density to the bronchovascular markings are helpful findings. Laboratory aids are of little help in establishing the diagnosis. The importance of pneumonitis of rheumatic fever origin as one of the serious manifestations of rheumatic fever activity cannot be overemphasized.

DURANT.

Servelle, M.: Collateral Channels in Venous Obliteration. *Arch. d. mal. du coeur.* 39: 2 (Jan.-Feb.), 1946.

The author states that there are few diseases of which knowledge is so limited as in the various forms of phlebitis. In reviewing his experiences with obliterative phlebitis of the extremities, he emphasizes the value of venography. This procedure, he points out, establishes a diagnosis which otherwise would be unrecognized until the appearance, years later, of varices, edema, and ulceration.

After obliteration of a large venous trunk, the circulation may be re-established by collateral channels developed from the branches of the main trunk or by recanalization. Obliterative phlebitis occurs in the femoral veins in 58 per cent of cases, in the popliteal veins in 22 per cent, in the iliac veins in 18 per cent, and in the calf veins in 8 per cent. Venography has demonstrated that primary varicosities are exceptional; varicosities are much more often secondary to venous obstruction. This fact explains the danger involved in sclerosing injections and surgical ablations which are performed blindly. What is commonly called the varicose ulcer is actually, in 80 per cent of cases, a postphlebotic ulcer.

LAPLACE.

Moses, W. R.: Ligation of the Inferior Vena Cava or Iliac Veins. A Report of 136 Operations. *New England J. Med.* 235: 2 (July 4), 1946.

The clinical differentiation between thrombophlebitis which seldom causes embolism and phlebothrombosis which commonly causes embolism is often extremely difficult. Various tests proposed for this purpose are very unreliable, as is phlebography, the popularity of which has declined considerably.

In the prevention of embolism from peripheral phlebothrombosis, surgery has many advantages over anticoagulant therapy. The latter may cause serious hemorrhage, especially from a pulmonary infarct or in pregnancy. Second, anticoagulants probably do not affect the clots already formed but simply prevent their propagation. Third, the time when anticoagulants may be discontinued is uncertain. Finally, an anticoagulant usually entails more expense and loss of time to the patient.

The indications adopted for ligation of the inferior vena cava are thrombophlebitis of the pelvic veins with pulmonary embolism; pulmonary embolus associated with prostatic tenderness of recent origin; pulmonary infarcts of obscure source; and venous occlusion in the lower extremities which would otherwise be treated by interruption of the femoral vein alone. Ligation of the vena cava is a more effective procedure than ligation of the femoral veins of which it is a complement rather than a substitute. Ligation of the vena cava has an advantage over iliac ligation in preventing embolism not only from the affected limb, but also from an unrecognized source in the opposite apparently normal limb.

The operation involves an extraperitoneal approach, may be completed in ten to fifteen minutes, and is attended by a minimum of postoperative discomfort and complications. Collateral venous return is much more adequate than one would suppose, and edema of the legs is less than that which follows ligation of the femoral vein. In the author's experience, edema following vena cava ligation has invariably been accompanied by evidence of pre-existence or recurrence of the disease process. The author reports thirty-five cases: twenty-one ligations of the inferior vena cava and fifteen of the iliac vein. (These figures include one case in which both veins were ligated.) Under present tentative indications, caval ligation would have been preferable in the fifteen cases of iliac ligation. Twenty-two patients survived and thirteen died.

LAPLACE.

Kempner, W.: Some Effects of the Rice Diet Treatment of Kidney Disease and Hypertension. *Bull. N. Y. Acad. Med.* 22: 358 (July), 1946.

The results of the use of the rice diet in 100 patients with primary kidney disease and in 222 patients with hypertensive vascular diseases are described. The diet is used in an attempt to reduce the amount of work required by the kidney cells, and thus reduce their demand for oxygen, in the presence of a pathologic condition which reduces the supply of oxygen.

The rice-fruit-sugar diet contains 2,000 calories, of which about 5 Gm. are fat and 20 Gm. are protein with not more than 0.2 Gm. of chloride and 0.15 Gm. of sodium. In seventy-nine patients with hypertensive cardiovascular disease, there was an average decrease in serum cholesterol of 57.3 milligrams.

In 203 of 322 patients in whom the rice diet was tried, there was objective improvement. Of the 100 patients with primary kidney disease, 65 per cent were improved. Of the 222 patients with hypertensive vascular disease, 62 per cent were improved. The author feels that dietary treatment should be tried before resorting to sympathectomy since the rice diet, if it proves to be ineffective, can simply be discontinued.

In 100 hypertensive patients studied electrocardiographically, there was a return to upright T waves in eleven of thirty-one patients with previously inverted T waves. In seventy-seven of eighty-seven patients the heart became smaller in size. In ten of the eighty-seven patients the heart became larger. Forty-four patients who had papilledema, hemorrhages, or exudates followed the rice diet for two months or longer. In all of them the retinopathy was arrested. In twenty of the forty-four patients, papilledema, hemorrhages, or exudates cleared up partially, and in twenty, completely.

NAIDE.

Piotti, A.: Paroxysmal Nodal Tachycardia in an Infant. *Cardiologia* 9: 121, 3: 1945.

The author reports the clinical and pathologic findings in an 11-month-old child observed over a period of ten months. He had three attacks of nodal tachycardia, lasting twenty-three days, forty-six days, and seven months. During the attacks, the heart was markedly enlarged, the rate ranged from 160 to 280 per minute, the blood pressure was 80/60, and anorexia, weakness, pallor, cyanosis, massive edema, and hepatomegaly were present. Between attacks the heart failure subsided spontaneously. The electrocardiogram taken during an attack showed negative P waves immediately preceding the QRS complexes. Between attacks the P waves were widened and notched. X-ray films showed tremendous enlargement of the left ventricle. There was a temporary response to ouabain pre sume, but no response to quinidine or gynergen was observed.

Digilanid was given throughout the course of treatment. The child had several bouts of rhinopharyngitis, one three months before onset of the tachycardia and others during his stay in the hospital. Death resulted from cardiac failure.

Autopsy revealed an interstitial myocarditis (Fiedler) located exclusively in the right auricle in the region where the connecting fibers from the coronary sinus (Kung's Brueckenfasern) join the Aschoff-Tawara node. The node itself was not involved. The entire conduction system was free from involvement. Serial sections through the entire heart failed to show other foci of myocarditis. There was severe dilatation and hypertrophy of all chambers. The nasopharyngitis was considered the possible etiologic factor of the myocarditis. The importance of serial sections is pointed out, as only part of the myocardium may be involved. The pathogenesis of the paroxysmal tachycardia is thought to be an alteration in the close and intimate contact between muscle fibers and nerve endings.

LENEL.

Chapuis, Jequier-Doze, and Werner: Newer Investigations on the Electrocardiogram in the Hypoxemic State. *Helvet. med. acta.* 19: 519, 1945.

Comparisons were made between postexercise and posthypoxemia electrocardiograms in patients suspected of having coronary artery disease. The authors conclude that changes indicative of coronary insufficiency will appear following inhalation of gas mixtures with low oxygen tension, whereas such changes will be lacking in the electrocardiogram following effort. In their experience, chest lead CR₁ proved to be the best derivation for demonstrating the characteristic changes. Alterations resulting from sympathetic overactivity provoked by the hypoxemic states could be abolished by intravenous injection of DHE (dihydroergotamine). The authors suggest, therefore, that this drug offers a simple means for improving the accuracy of the "hypoxemia test" in differentiating changes due to structural cardiac disease from those due to reflex augmentations of adrenergic activity.

WENDKOS.

Thompson, L. E., and Gerstl, B.: Thromboangiitis of Pulmonary Vessels Associated With Aneurysm of Pulmonary Artery: Report of a Case. *Arch. Int. Med.* 77: 614 (June), 1946.

This paper reports a case in which an aneurysm of the right pulmonary artery of more than 10 cm. in diameter developed within a period of three months and was associated with thromboangiitis of both pulmonary arteries and veins. The underlying cause of the changes in the pulmonary vessels was uncertain. *Streptococcus viridans* infection, syphilis, and congenital malformation were apparently excluded by the clinical course and by the laboratory and necropsy observations. The possibility was suggested that the lesions represented a variety of periarteritis nodosa, but this diagnosis could not be made with certainty.

BELLET.

Westerman, A.: On Calcifying, Scarifying Inflammations of the Pericardial Sac, and the Results of Operative Management. *Arch. f. klin Chir.* 205: 549 (May 18), 1944.

Fifty-three patients with chronic constrictive and/or adhesive pericarditis who had total pericardiectomies by Schmieden and medical management by Volhard at the Frankfurt Clinic are reported. There were thirty-seven males and sixteen females; the majority were in the second to fourth decades of life at the time of operation. One-third of thirty-four patients operated on before 1939 made complete recoveries; one quarter showed definite improvement. Since 1939, slightly better results were observed: 64.2 per cent recovered or showed definite improvement.

Though the immediate operative mortality remains high, it is believed that total pericardiectomy gives much better results than the precordial cardiolysis of Brauer, although the mortality of the latter procedure is much lower at the operating table and even for a year postoperatively. Most autopsied cases showed a mixture of the constrictive and adhesive forms of chronic

pericarditis with little or no evidence of active infection. Aschoff bodies were never found and cultures were always negative, though occasionally histologic tuberculosis was present. The general impression was of a burnt-out process whose etiology was usually only suggested by the past medical history. This included some acute infection (rheumatic fever, sore throat, grippe, otitis, or pneumonia) in 68 per cent and tuberculosis in 9.4 per cent. In 19 per cent of the cases there was no clue as to the etiology.

The various types of acute and chronic pericarditis are described. The clinical picture and pathologic physiology of the adhesive variety (accretio cordis) with the systolic rib retraction and diastolic heart recoil (Brauer's sign) is distinguished from the constrictive variety (concretio cordis) with its interference with diastole and resultant venous congestion. However, this differentiation is clear cut more often clinically than pathologically. Both forms affect the function of the auricles and the right ventricle before the left ventricle, presumably because of the latter's thicker walls and higher pressure.

The importance of early operation while the heart muscle retains enough adaptability to function without its calcific encasement is stressed, as is pre- and postoperative medical care. The clinical diagnosis was often difficult.

The literature on experimental production of chronic pericarditis and the various forms of operative interference is reviewed. Pertinent data concerning each of the fifty-three cases are tabulated, with particular emphasis on the results of the operative procedure.

SAYEN.

McCutchen, G. T.: Varicosities of the Lower Extremity. Am. J. Surg. 72: 63 (July), 1946.

Several methods of examining patients with varicose veins are re-emphasized. The author also describes a method for locating incompetent communicating veins or "perforators" as an operation on the venous system progresses. Patency of the deep venous circulation is determined by application of a tourniquet at the upper thigh for the great saphenous vein and just below the knee for the lesser saphenous. The tourniquet is applied with the patient in the upright position so that the veins are distended at the beginning of the test. The patient is allowed to walk a few steps. If the veins become less tense, the deep circulation is patent.

The method of locating incompetent communicating veins during an operation consists in placing the patient in the reverse Trendelenburg position (legs and trunk down) and advancing a tourniquet from below upward on the leg. At the points where perforators are suspected, the vein is exposed and severed between clamps. The perforator, if it is found, is treated in the same manner. Preliminary testing may be carried out by the application of two tourniquets at short distances from each other while the Trendelenburg position is assumed, followed by assumption of the reverse Trendelenburg position. However, it is believed that the ligation as described acts in a more effective manner than the lower tourniquet in stopping confusing flow from the distal points of the vein. A number of illustrations accompany the description of this method.

The extreme reverse Trendelenburg position should be assumed and maintained for five to ten minutes after all ligations are completed. If dilatation of any of the veins becomes manifest it may be assumed that an incompetent perforator has been overlooked and further search is in order.

NAIDE.

Cosgrove, Jr., C. E., and Kaump, D. H.: Endocardial Sclerosis in Infants and Children. Am J. Clin. Path. 16: 322 (May), 1946.

The authors review the theories of the pathogenesis of endocardial sclerosis in infants and children and describe the pathologic findings listed by other observers. These findings are also compared with the findings in six cases of their own. Compositely these varied grossly from simple thickening and opacity of the endocardium to severely distorted valves in extreme instances. The myocardial changes seemed to parallel the extent of the endocardial involvement. The heart generally was enlarged due to myocardial fibrosis, myocardial hypertrophy, and dilatation of the ventricles. The coronary arteries were normal.

Microscopically the endocardial thickening was composed chiefly of collagenous connective tissue with some increase in elastic tissue, which in many areas extended as fingerlike projections between the myocardial fibers. Occasionally the thickening was nodular and resembled myxomatous tissue or possessed a cartilaginous-like component at the base of the valves. Occasional vessels in the endocardium showed much narrowing due to endothelial fibrosis. The myocardium frequently was markedly vascular and showed numerous areas of degeneration, varying from loss of muscle striation to necrosis. In none of the six cases was there definite indication of inflammatory changes as evidenced by myocardial giant cells or infiltration with lymphocytes or polymorphonuclear cells. The myocardial changes were particularly prominent in the papillary muscles and less frequent in the ventricular septum. Except for the Thebesian vessels, the veins of the myocardium were generally normal and no thromboses were found. When myocardial lesions occurred, they resembled infarctions rather than inflammatory lesions. This, together with the relative or complete occlusion of the smaller mural arterial and venous channels, inclined the authors to accept the probability that primary endocardial sclerosis is congenital. This impression was strengthened by the absence of evidences of inflammatory cell infiltration, the marked edema, the relatively young connective tissue, the lack of advancing proliferation of connective tissue, and the minimal tendency toward vascularization. Because of the high proportion of recorded illness in the mothers of these infants, the authors suggest that such illnesses of the mother during pregnancy, particularly early pregnancy, may be a factor in the production of endocardial sclerosis.

They conclude that the gross and microscopic characteristics of the lesions indicate that endocardial sclerosis in infants is a form of congenital heart disease.

MERANZE.

Estes, J. E., and Keith, N.: Hypothyroidism and Mild Myxedema from Thiocyanate Intoxication. Am. J. Med. 1: 45 (July), 1946.

Thiocyanate therapy in a 62-year-old woman with hypertension caused definite symptoms of hypothyroidism and mild myxedema. Cardiac enlargement, demonstrated by roentgenographic examination, regressed upon withdrawal of the drug. During thiocyanate intoxication the electrocardiogram displayed an abnormally low total voltage of the QRS complexes and inverted, diphasic, and isoelectric T waves in various leads. The QRS complexes reverted to normal total voltage and the T waves became upright and of normal amplitude in all leads upon recovery from the intoxication.

The ultimate effects of hypothyroidism upon the heart are discussed. The cardiac enlargement seen in the teleoroentgenogram is generalized, involves all four chambers, and is currently viewed as a dilatation rather than a hypertrophy or pericardial effusion. The electrocardiographic changes are attributed to a reduction in cardiac conductivity rather than to reduction in skin conductivity.

FRIEDLAND.

Stewart, H. J., Evans, W. F., Brown, H. and Gerjuoy, J. R.: Peripheral Blood Flow, Rectal and Skin Temperature in Congestive Heart Failure: The Effects of Rapid Digitalization in This State. Arch. Int. Med. 77: 643 (June), 1946.

It has been observed by various investigators that the temperature of the surface of cardiac patients is lower than in normal individuals, while that of patients with infectious fever is higher than normal. Certain experimental data point to a decrease in the amount of blood allotted to the peripheral blood flow in congestive heart failure.

Peripheral blood flow was measured in fifteen patients exhibiting congestive heart failure before and after administration of strophanthin K and digitaline Nativelle intravenously. Measurements of rectal and of skin temperature were recorded. Electrocardiograms, circulation time, and venous pressure were made to correlate with the measurements of the peripheral blood flow.

It was observed that the amount of blood flow allotted for the whole periphery of the body is within the normal range during heart failure as compared with the amount in normal subjects at

the same environmental temperature. Even though the same amount of blood is allotted to the peripheral circulation in heart failure, it is insufficient because of its slowed velocity in a vascular tree that is dilated to maintain an adequate elimination of heat in the face of the metabolic demands, so that the internal temperature of the body (rectal temperature) rises.

After the administration of strophanthin K intravenously, the peripheral blood flow increases. With the allocation of more blood to the periphery, the temperature of the skin rises and the body can now lose more heat by way of the skin, and its internal temperature (rectal temperature) falls slightly but does not usually reach normal levels over the intervals studied by the author.

BFLLET.

Radner, S.: An Attempt at the Roentgenologic Visualization of Coronary Blood Vessels in Man. *Acta. radiol.* 26: 497 (No. 6), 1945.

Using a modified technique of sternal puncture, a needle was inserted into the anterior upper mediastinum and then, under fluoroscopic guidance, into the ascending aorta. Twenty to 30 c.c. of thorotrast solution were injected rapidly. Five patients were studied by the technique. Of films taken in three cases, only one proved satisfactory. This film is reproduced and shows the aortic valves, the dye in the sinuses of Valsalva, and vague shadows of what appear to be the first portions of the coronary arteries. One patient developed mediastinal emphysema, and in one the needle penetrated the posterior aortic wall so that thorotrast was deposited in the pericardium, setting up a purulent inflammation which only very gradually resolved. At present, the problem of a satisfactory contrast medium has not been adequately solved.

SÄYEN.

Laudis, E. M., Brown, E., Fauteaux, M., and Wise, C.: Central Venous Pressure in Relation to Cardiac "Competence," Blood Volume, and Exercise. *J. Clin. Investigation* 25: 237 (March), 1946.

Evidence was obtained in anesthetized dogs to support the "back pressure" hypothesis of congestive heart failure. The dogs were exercised by electrical stimulation of all four limbs once each second. During control exercise, while cardiac function was normal, venous (right auricular) pressure, after a transient rise, fell to 96 mm. of water. After ligation of coronary arteries, resting venous pressure did not rise, but exercise was accompanied either by a decline in venous pressure, which was always less pronounced than that observed during control exercise, or by a definite rise. Electrically induced auricular fibrillation caused only slight rises in venous pressure, whereas combined auricular fibrillation plus exercise elevated venous pressure to higher levels. On the contrary, elevated resting venous pressure due to cardiac tamponade was lowered by exercise as in the control experiments, unless prior myocardial damage had reduced cardiac competence. Moreover, when venous pressure had been increased to extremely high levels by infusions of citrated whole blood or of Ringer's solution amounting to 50 per cent or more of the calculated blood volume, exercise was still capable of reducing the venous pressure.

A final set of experiments showed that during asphyxia, agonal arterial constriction effected a redistribution of approximately 20 per cent of the total circulating blood volume from the arterial to the venous bed. After auricular fibrillation and prolonged exercise, the blood redistributed to the venous bed during asphyxia amounted to about one-half the usual quantity, indicating that filtration had occurred during the high venous pressure incident to the combination of auricular fibrillation and exercise.

These experimental data provide the fundamentals for the development of a hypothesis of chronic congestive failure based upon the "back pressure" concept. Patients with reduced cardiac competence develop increased venous pressure during muscular activity. Effective circulating blood volume diminishes consequent to both sequestration of blood in the venous system and excessive filtration. Compensatory vasoconstriction occurs and is accompanied by reduced renal excretion of sodium and water and overproduction of erythrocytes and plasma proteins. Repeated muscular activity leads to secondary plethora or hypervolemia and eventuates in the typically high resting venous pressure of chronic congestive failure.

FRIEDLAND.

Book Reviews

LE TUMEURS ET LES POLYPES DU COEUR—ETUDE ANATOMO-CLINIQUE: By Dr. Ivan Mahaim.

Monographie de l'Institut d'Anatomie pathologique de l'Université de Lausanne. F. Röth et Cie, Editeurs, Lausanne; Masson et Cie, Editeurs, Paris, 1945. With 568 pages and 67 illustrations.

This book includes an exhaustive description and extensive discussion, with a fairly complete bibliography, of cases of primary and secondary tumors of the heart and pericardium. The author draws attention to the more frequent occurrence of these tumors than has been recognized hitherto by most clinicians or even many pathologists. He gives in detail the clinical signs and symptoms that should lead to a premortem diagnosis of these tumors, especially in certain locations, and emphasizes the importance of considering this diagnosis in all cases of otherwise unexplained cardiac insufficiency. Much attention is paid in this book to the subject of polypoid growths, especially those within the left atrium or auricle, some of which are not truly neoplastic.

The benign polyps are the subject of extensive description and discussion, because the author believes that they may kill by obstructing the flow of blood from atrium to ventricle, either by valvular occlusion, or by atrial obliteration, and that a cure might be effected by surgical removal of these growths. In his opinion these tumors offer a challenge to the surgery of the future, and he even gives in detail the possible techniques that have occurred to him. The possibility of successful excision of some types of tumor of the pericardium is also considered.

The occurrence of embolism associated with intracardiac growths, especially of the polypoid type, is emphasized, and the author draws attention to the importance of embolectomy in cases of peripheral embolism. Such emboli are accessible to biopsy or removal, and histologic examination of the embolus can prove to be a great aid in the diagnosis of intracardiac tumors. In his experience, myxomatous tissue in a peripheral embolus in the systemic circulation means, almost unquestionably, the existence of a polyp in the left atrium or auricle; thrombotic tissue may mean a thrombotic polyp or myxomatous polyp covered with thrombus at the tip, or a mural thrombus in the left atrium, or, much less likely, in the left ventricle. He gives in full detail the clinical signs of an obstructive mass in the left atrium but states that there are no certain signs of an occlusive polyp in the right atrium. Particular emphasis is placed on the importance of basic simple clinical observations, and the inadequacy of some of the special and more expensive methods of investigation, for the purpose of the clinical diagnosis of tumors of heart and pericardium.

The book is well written and covers very thoroughly the description and discussion of all the known benign and malignant tumors of both heart and pericardium. It is an important and timely contribution to this subject and certainly constitutes a challenge to those who are interested in heroic surgery. It is his hope that, while surgeons are learning techniques for the possible excision of many of these tumors, physicians will busy themselves with learning how to make an early clinical diagnosis of what he considers an important cause of cardiac insufficiency.

HARRY GOLDBLATT.

American Heart Association, Inc.

1790 BROADWAY AT 58TH STREET, NEW YORK, N. Y.

DR. ROY W. SCOTT
President

DR. HOWARD F. WEST
Vice-President

DR. GEORGE R. HERRMANN
Treasurer

DR. HOWARD B. SPRAGUE
Secretary

BOARD OF DIRECTORS

DR. EDGAR V. ALLEN Rochester, Minn.
DR. GRAHAM ASHER Kansas City, Mo.
*DR. ARLIE R. BARNES Rochester, Minn.
DR. ALFRED BLALOCK Baltimore
*DR. WILLIAM H. BUNN Youngstown, Ohio
DR. CLARENCE DE LA CHAPELLE New York City
*DR. TINSLEY R. HARRISON Dallas
DR. GEORGE R. HERRMANN Galveston
DR. T. DUCKETT JONES Boston
DR. LOUIS N. KATZ Chicago
DR. SAMUEL A. LEVINE Boston
DR. GILBERT MARQUARDT Chicago
*DR. H. M. MARVIN New Haven
*DR. EDWIN P. MAYNARD, JR. Brooklyn
*DR. THOMAS M. McMILLAN Philadelphia
DR. JONATHAN MEAKINS Montreal, Can.
DR. E. STERLING NICHOL Miami

DR. HAROLD E. B. PARDEE New York City
DR. WILLIAM B. PORTER Richmond, Va.
*DR. DAVID D. RUTSTEIN New York City
*DR. JOHN J. SAMPSON San Francisco
DR. ROY W. SCOTT Cleveland
*DR. HOWARD B. SPRAGUE Boston
DR. GEORGE F. STRONG Vancouver, B. C., Can.
DR. WILLIAM D. STROUD Philadelphia
DR. HOMER F. SWIFT New York City
DR. WILLIAM P. THOMPSON Los Angeles
DR. HARRY E. UNGERLEIDER New York City
*DR. HOWARD F. WEST Los Angeles
DR. PAUL D. WHITE Boston
DR. FRANK N. WILSON Ann Arbor
*DR. IRVING S. WRIGHT New York City
DR. WALLACE M. YATER Washington, D. C.

*Executive Committee.

DR. H. M. MARVIN, *Acting Executive Secretary*

ANNA S. WRIGHT, *Office Secretary*

Telephone, Circle 5-8000

THE American Heart Association is the only national organization devoted to educational work relating to diseases of the heart. Its activities are under the control and guidance of a Board of Directors composed of thirty-three eminent physicians who represent every portion of the country.

A central office is maintained for the coordination and distribution of important information. From it there issues a steady stream of books, pamphlets, charts, films, lantern slides, and similar educational material concerned with the recognition, prevention, or treatment of diseases of the heart, which are now the leading cause of death in the United States. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning the circulation of blood and lymph. Any physician or investigator may become a member of the section after election to the American Heart Association and payment of dues to that organization.

The income from membership and donations provides the sole financial support of the Association. Lack of adequate funds seriously hampers more intensive educational activity and the support of important investigative work.

Annual membership is \$5.00. Journal membership at \$11.00 includes a year's subscription to the AMERICAN HEART JOURNAL (January-December) and annual membership in the Association. The Journal alone is \$10.00 per year.

The Association earnestly solicits your support and suggestions for its work. Membership application blanks will be sent on request. Donations will be gratefully received and promptly acknowledged.

AMERICAN HEART JOURNAL

For the Study of the
CIRCULATION



©Am. Ht. Assn.

PUBLISHED MONTHLY

Under the Editorial Direction of
THE AMERICAN HEART ASSOCIATION

THOMAS M. McMILLAN
Editor-in-Chief

ASSOCIATE EDITORS

WALLACE M. YATER
SAMUEL BELLET
LOUIS B. LAPLACE

EDITORIAL BOARD

EDGAR V. ALLEN
ALFRED BLALOCK
CLARENCE E. DE LA CHAPELLE
HARRY GOLDBLATT
TINSLEY R. HARRISON
T. DUCKETT JONES
LOUIS N. KATZ
EUGENE M. LANDIS

JOHN K. LEWIS
H. M. MARVIN
JONATHAN C. MEAKINS
ROY W. SCOTT
ISAAC STARR
PAUL D. WHITE
FRANK N. WILSON
CHARLES C. WOLFERTH

IRVING S. WRIGHT

VOLUME 32
JULY-DECEMBER, 1946

St. Louis
THE C. V. MOSBY COMPANY
1946

COPYRIGHT 1946, BY THE C. V. MOSBY COMPANY

(All rights reserved)

Printed in the
United States of America

Press of
The C. V. Mosby Company
St. Louis

INDEX TO VOLUME 32

AUTHORS INDEX

A

- ABRAMSON, DAVID I., LERNER, DAVID, SHUMACKER, HARRIS B., JR., AND HICK, FORD K. Clinical picture and treatment of the later stage of trench foot, 52
- ALEXANDER, HOWARD. (See Simonson, Alexander, Henschel, and Keys), 202
- ALTURE-WERBER, ERNA. (See Loewe, Rosenblatt, and Altüre-Werber), 327
- ANDERSON, MILTON W., BARKER, NELSON W., AND SELDON, THOMAS H. A clinical evaluation of powdered human blood cells in the treatment of ulcers of the extremities associated with vascular disorders, 754

B

- BAER, SAMUEL. (See Loewenberg and Baer), 653
- BALDWIN, ELEANOR DEF., MOORE, LUCILLE V., NOBLE, ROBERT P. (with technical assistance of PATTERSON, MICHAEELEN, AND HARNSBERGER, DORIS M.). The demonstration of ventricular septal defect by means of right heart catheterization, 152
- BARKER, NELSON W. (See Anderson, Barker, and Seldon), 754
- BARKER, PAUL S. (See Wilson, Johnston, Rosenbaum, and Barker), 277
- BEASER, S. B., AND RODRIGUEZ-MOLINA, R. Electrocardiographic changes occurring during treatment with fuadin solution, 634
- BEISSINGER, HEINZ F. (See Weinberg and Beissinger), 665
- BEMBENISTA, J. K. Cor biloculare, 394
- BIÖRCK, GUNNAR. Anoxemia and exercise tests in the diagnosis of coronary disease, 689
- BLAND, EDWARD F. Rheumatic fever and rheumatic heart disease in the North African and Mediterranean Theater of Operations, United States Army, 545
- BOYER, NORMAN H. (See Nay and Boyer), 222
- BROWN, N. WORTH. (See Ellis and Brown), 364
- BURCH, G. E. Influence of variations in atmospheric temperature and humidity on the rates of water and heat loss from the respiratory tract of patients with congestive heart failure living in a subtropical climate, 190

- . The rates of water and heat loss from the respiratory tract of patients with congestive heart failure who were from a subtropical climate and resting in a comfortable atmosphere, 88
- , AND KIMBALL, J. LEROY. Notes on the similarity of QRS complex configurations in the Wolff-Parkinson-White syndrome, 560
- BUTTERWORTH, SCOTT, AND POINDEXTER, CHARLES A. The esophageal electrocardiogram in arrhythmias and tachycardias, 681

C

- CATHCART, RICHARD T. (See Spain and Cathcart), 659
- CLARK, MARDELLE L. (See Eanes, McGill, and Clark), 504
- COFFEN, CHARLES W., AND SCARF, MAXWELL. Acute pericarditis simulating coronary artery occlusion, 515
- COOMBS, F. S. (See Warren, Higley, and Coombs), 311

D

- DELEVETT, ALLEN F., AND POINDEXTER, CHARLES A. Plasma concentrations of quinidine with particular reference to therapeutically effective levels in two cases of paroxysmal nodal tachycardia, 697
- DIPALMA, JOSEPH R., AND MAgOVERN, JOHN J. Disadvantages of thiouracil treatment of angina pectoris, 494
- DONOVAN, MAURICE A. Pain of unusual duration due to progressive coronary occlusion with associated mediastinal tumor, 786

E

- EANES, RICHARD H., MCGILL, KENNETH H., AND CLARK, MARDELLE L. Cardiovascular defects in Selective Service registrants, 504
- EIDLOW, S., AND MACKENZIE, ELEANOR R. Anomalous origin of the left coronary artery from the pulmonary artery; report of a case diagnosed clinically and confirmed by necropsy, 243
- ELLIS, GEORGE M., AND BROWN, N. WORTH. Parasternal leads in tricuspid insufficiency, 364

F

- FASCIOLO, J. C. (See Suárez, Fasciolo, and Taquini), 339
 —. (See Taquini and Fasciolo), 357
 FULTON, FRANK T. (See Zimdahl and Fulton), 117

G

- GEIGER, ARTHUR J., AND GOERNER, JESSAMINE R. A simplified and more standardized technique for recording multiple precordial electrocardiograms, 163
 GERNANDT, B., AND NYLIN, G. The relation between circulation time and the amount of the residual blood of the heart, 411
 GOERNER, JESSAMINE R. (See Geiger and Goerner), 163
 GRANT, HAROLD. (See Reichsman and Grant), 438
 —, AND REICHSMAN, FRANCIS. The effects of the ingestion of large amounts of sodium chloride on the arterial and venous pressures of normal subjects, 704
 GREENE, RALPH C. Combined sulfonamide and diphtheritic myocarditis in cutaneous diphtheria, 250

H

- HARKEN, DWIGHT E., AND ZOLL, PAUL M. Foreign bodies in and in relation to the thoracic blood vessels and heart. III. Indications for the removal of intracardiac foreign bodies and the behavior of the heart during manipulation, 1
 HARNSBERGER, DORIS M. (See Baldwin, Moore, Noble, Patterson, and Harnsberger), 152
 HARRIS, RAYMOND. (See Scherf and Harris), 443
 HECHT, HANS H. Potential variations of the right auricular and ventricular cavities in man, 39
 HENSCHEL, AUSTIN. (See Simonson, Alexander, Henschel, and Keys), 202
 HEYER, HOWARD E. Abnormalities of the respiratory pattern in patients with cardiac dyspnea, 457
 HICK, FORD K. (See Abramson, Lerner, Shumacker, and Hick), 52
 HIGLEY, C. S. (See Warren, Higley, and Coombs), 311
 HILL, R. F. The construction of the cardiac vector, 72
 HUNT, HOMER H., AND WELLER, CARL V. The syndrome of abdominal aortic aneurysm rupturing into the gastrointestinal tract, 571

J

- JOHNSTON, FRANKLIN D. (See Rosenbaum, Wilson, and Johnston), 135
 —. (See Wilson, Johnston, Rosenbaum, and Barker), 277

- JONES, REVERDY H., JR., AND MOORE, WILLIAM W. Purpuric manifestations of rheumatic fever and acute glomerulonephritis, 529

K

- KEYS, ANCEL. (See Simonson, Alexander, Henschel, and Keys), 202
 KIMBALL, J. LEROY. (See Burch and Kimball), 560

L

- LENER, DAVID. (See Abramson, Lerner, Shumacker, and Hick), 52
 LINDSAY, STUART. The heart in primary systemic amyloidosis, 419
 LITTMANN, DAVID. Persistence of the juvenile pattern in precordial leads of healthy adult Negroes, with report of electrocardiographic survey on three hundred Negro and two hundred white subjects, 370
 —, AND TARNOWER, HERMAN. Wolff-Parkinson-White syndrome, 100
 LOEWE, LEO, ROSENBLATT, PHILIP, AND ALTURE-WERBER, ERNA. A refractory case of subacute bacterial endocarditis due to *Veillonella gazogenes* clinically arrested by a combination of penicillin, sodium para-aminohippurate, and heparin, 327
 LOEWENBERG, SAMUEL A., AND BAER, SAMUEL. Aneurysm of the descending thoracic aorta, 653
 LOUBE, SAMUEL D. (See Manchester and Loubé), 215

M

- MCGILL, KENNETH H. (See Eanes, McGill, and Clark), 504
 MCGOVERN, JOHN J. (See DiPalma and McGovern), 494
 MACKENZIE, ELEANOR R. (See Eidlow and Mackenzie), 243
 MANCHESTER, BENJAMIN, AND LOUBE, SAMUEL D. The velocity of blood flow in normal pregnant women, 215
 MASTER, ARTHUR M. Right-sided aorta with atypical coarctation involving only the left subclavian artery; hypertension, 778
 MILLER, ISIDORE. (See Russek, Rath, Zohman, and Miller), 468
 MOORE, LUCILLE V. (See Baldwin, Moore, Noble, Patterson, and Harnsberger), 152
 MOORE, WILLIAM W. (See Jones and Moore), 529
 DE MOURA, JOSE PROENCA PINTO. Complete auriculoventricular block and bundle branch block with intercurrent auricular flutter, 794

N

- NAY, RICHARD M., AND BOYER, NORMAN H. Acute pericarditis in young adults, 222
 NOBLE, ROBERT P. (See Baldwin, Moore, Noble, Patterson, and Harnsberger), 152

- NORRIS, ROBERT F., AND POTE, HARRY H. Hypertrophy of the heart of unknown etiology in young adults: report of four cases with autopsies, 599
- NOTH, PAUL H. Electrocardiographic patterns in penetrating wounds of the heart, 713
- NYLIN, G. (See Gernandt and Nylin), 411

O

- OYSTER, JOSEPH M. (See Tandowsky, Oyster, and Silverglade), 617

P

- PATTERSON, MICHAEELEN. (See Baldwin, Moore, Noble, Patterson, and Harnsberger), 152
- PAULL, ROSS. The neurovascular syndrome as manifested in the upper extremities, 32
- PENNER, SIDNEY L. (See Peters and Penner), 645
- PETERS, MICHAEL, AND PENNER, SIDNEY L. Orthostatic paroxysmal ventricular tachycardia, 645
- POINDEXTER, CHARLES A. (See Butterworth and Poindexter), 681
- . (See Delevett and Poindexter), 697
- POTE, HARRY H. (See Norris and Pote), 599

Q

- QUINN, ROBERT W. The incidence of rheumatic fever and heart disease in school children in Dublin, Georgia, with some epidemiological and sociological observations, 234

R

- RATH, MAURICE M. (See Russek, Rath, Zohman, and Miller), 468
- REICHSMAN, FRANCIS. (See Grant and Reichsman), 704
- , AND GRANT, HAROLD. Some observations on the pathogenesis of edema in cardiac failure, 438
- RODRIGUEZ-MOLINA, R. (See Beaser and Rodriguez-Molina), 634
- ROGERS, H. MILTON. Bilateral pulmonary infarction and pneumothorax complicating hypertensive, coronary heart disease with myocardial infarction: report of a case, 519
- ROSENBAUM, FRANCIS F. (See Wilson, Johnston, Rosenbaum, and Barker), 277
- , WILSON, FRANK N., AND JOHNSTON, FRANKLIN D. The precordial electrocardiogram in high lateral myocardial infarction, 135
- ROSENBLATT, PHILIP. (See Loewe, Rosenblatt, and Altire-Werber), 327
- RUSSEK, HENRY I., RATH, MAURICE M., ZOHMAN, BURTON L., AND MILLER, ISIDORE. The influence of age on blood pressure, 469
- RYTAND, DAVID A. An auricular diastolic murmur with heart block in elderly patients, 579

S

- SCARF, MAXWELL. (See Coffen and Scarf), 515
- SCHERF, DAVID, AND HARRIS, RAYMOND. Coronary sinus rhythm, 443
- SCHLICHTER, J. G. Studies on the vascularization of the aorta. I. The vascularization of the aorta in the normal dog, 770
- SELDON, THOMAS H. (See Anderson, Barker, and Seldon), 754
- SHUMACKER, HARRIS B. (See Abramson, Lerner, Shumacker, and Hick), 52
- SILVERGLADE, ALEXANDER. (See Tandowsky, Oyster, and Silverglade), 617
- SILVERMAN, JACOB J. The incidence of palpable dorsalis pedis and posterior tibial pulsations in soldiers, 82
- SIMONSON, ERNST, ALEXANDER, HOWARD, HENSCHEL, AUSTIN, AND KEYS, ANCEL. The effect of meals on the electrocardiogram in normal subjects, 202
- SMITH, LESLIE B. Paroxysmal ventricular tachycardia followed by electrocardiographic syndrome, 257
- SPAIN, DAVID M., AND CATHCART, RICHARD T. Heart block caused by fat infiltration of the interventricular septum (cor adiposum), 659
- SUAREZ, J. R. E., FASCILOLO, J. C., AND TAQUINI, A. C. Cardiac output in heart failure, 339
- SUAREZ, RAMON M., AND SUAREZ, RAMON M., JR. The T wave of the precordial electrocardiogram at different age levels, 480
- SUAREZ, RAMON M., JR. (See Suárez and Suárez, Jr.), 480
- SWENSON, ROY E. Parenteral vitamin B as an agent for determining the arm-to-tongue circulation time, 612

T

- TANDOWSKY, RALPH M., OYSTER, JOSEPH M., AND SILVERGLADE, ALEXANDER. The combined use of lanatoside C and quinidine sulfate in the abolition of established auricular flutter, 617
- TAQUINI, A. C. (See Suárez, Fasciolo, and Taquini), 339
- , AND FASCILOLO, JUAN CARLOS. Renin in essential hypertension, 357
- TARNOWER, HERMAN. (See Littmann and Tarnower), 100

W

- WARREN, HARRY A., HIGLEY, C. S., AND COOMBS, F. S. The effect of salicylate on acute rheumatic fever, 311
- WEINBERG, TOBIAS, AND BEISSINGER, HEINZ F. Syphilitic gummatous aortitis as the cause of coronary artery ostial stenosis and myocardial infarction, 665
- WELLER, CARL V. (See Hunt and Weller), 571
- WILSON, FRANK N. (See Rosenbaum, Wilson, and Johnston), 135

-----, JOHNSTON, FRANKLIN D., ROSENBAUM, FRANCIS F., AND BARKER, PAUL S. On Einthoven's triangle, the theory of unipolar electrocardiographic leads, and the interpretation of the precordial electrocardiogram. 277

WRIGHT, IRVING S. Experiences with dicumaryl (3,3'-methylene-bis-[4-hydroxycoumarin]) in the treatment of coronary thrombosis with myocardial infarction. 20

Y

YOUNG, DENNISON. Electrocardiographic changes occurring during upper respiratory infections, 383

Z

ZIMDAHL, WALTER T., AND FULTON, FRANK T. Transient ventricular fibrillation, 117

ZOHMAN, BURTON L. (See Russek, Rath, Zohman, and Miller), 468

ZOLL, PAUL M. (See Harken and Zoll), 1

SUBJECT INDEX

A

Abdominal aortic aneurysm rupturing into gastrointestinal tract, syndrome of (Hunt and Weller), 571
 aortography, retrograde, 406*

Abnormalities of respiratory pattern in patients with cardiac dyspnea (Heyer), 457

Acetylcholine, stimulating action of, on heart, 408*

Acute pericarditis in young adults (Nay and Boyer), 222

Addison's disease, disturbance of pacemaker and of conduction in, 270*

Adults, young, acute pericarditis in (Nay and Boyer), 222

African, North, and Mediterranean Theater of Operations, United States Army, rheumatic fever and rheumatic heart disease in (Bland), 545

Age, influence of, on blood pressure (Russek et al.), 468
 levels, different, T wave of precordial electrocardiogram at (Suárez and Suárez, Jr.), 480

Albumin, human, concentrated, in treatment of shock, 672*

Alcohol in treatment of angina pectoris, 403*

American Heart Association, expanded program of, for 1947, 679

Amyloidosis myocardii, 127*
 systemic, primary, heart in (Lindsay), 419

Anemia, cardiovascular system in, with note on particular abnormality of sickle cell anemia, 270*

Aneurysm, aortic, abdominal, rupturing into gastrointestinal tract, syndrome of (Hunt and Weller), 571
 arteriovenous, following surgical operations, 805*
 of descending thoracic aorta (Loewenberg and Baer), 653
 ventricular, longevity with; report of case with survival period of fifteen years, 402*

Aneurysms, traumatic, of extremities, 407*

Angina pectoris, alcohol in treatment of, 403*
 application to study of; circulatory changes following injection of hypertonic saline solution, 129*
 disadvantages of thiouracil treatment of (DiPalma and MaGovern), 494
 life expectancy in, 269*
 testosterone in, 806*

Announcements, 133

Anoxemia and exercise tests in diagnosis of coronary disease (Biörck), 689
 experimental cyanosis and, effects of artificial ductus arteriosus on, 407*

Aorta, right-sided, with atypical coarctation involving only left subclavian artery; hypertension (Master), 778
 roentgenological picture of coarctation of, and its anatomical basis, 127*
 slowly progressive occlusive thrombosis of abdominal portion of, 127*
 studies on vascularization of; I. Vascularization of aorta in normal dog (Schlichter), 770
 thoracic, descending, aneurysm of (Loewenberg and Baer), 653

Aortic aneurysm, abdominal, rupturing into gastrointestinal tract, syndrome of (Hunt and Weller), 571
 coarctation, new indirect radiologic sign in diagnosis of, by means of superior retrograde aortography, 274*
 perforation secondary to carcinoma of esophagus, genesis of, 674*
 stenosis due to calcified syphilitic valvulitis, 403*
 valve, bicuspid, diagnosed during life, 401*
 valves, rupture of, due to effort, 273*

Aortitis, gummatous, syphilitic, as cause of coronary artery ostial stenosis and myocardial infarction (Weinberg and Beissinger), 665

Aortography, abdominal, retrograde, 406*
 retrograde, superior, new indirect radiologic sign in diagnosis of aortic coarctation by means of, 274*

Arm-to-tongue circulation time, parenteral vitamin B as agent for determining; Part I (Swenson), 612

Army, United States, rheumatic fever and rheumatic heart disease in North African and Mediterranean Theater of Operations (Bland), 545

Arrhythmias, acute, treatment of, during anesthesia by intravenous procaine, 270*
 and tachycardias, esophageal electrocardiogram in (Butterworth and Poindexter), 681

Arterial and venous pressures of normal subjects, effects of ingestion of large amounts of sodium chloride on (Grant and Reichsman), 704
 disease, peripheral, 125*
 pulse pressure, relation of, to arteriovenous oxygen difference, especially in arterial hypertension, 126*

Arteriosclerosis obliterans, relation of tobacco smoking to, in diabetes mellitus, 400*

Arteriovenous aneurysm following surgical operations, 805*

An asterisk () after a page number indicates the reference is an abstract and not an original article.

Arteriovenous--Cont'd

- oxygen difference, relation of arterial pulse pressure to, especially in arterial hypertension, 126*
- Arteritis, temporal, generalized vascular disease, 406*
- Artery, coronary, left, anomalous origin of, from pulmonary artery; report of case diagnosed clinically and confirmed by necropsy (Eidlow and Mackenzie), 243
 - occlusion, acute pericarditis simulating (Coffen and Scarf), 515
 - ostial stenosis and myocardial infarction, syphilitic gummatous aortitis as cause of (Weinberg and Beissinger), 665
 - pulmonary, anomalous origin of left coronary artery from; report of case diagnosed clinically and confirmed by necropsy (Eidlow and Mackenzie), 243
 - subclavian, left, right-sided aorta with atypical coarctation involving only; hypertension (Master), 778
- Atheromatosis in dogs following repeated intravenous injections of hydroxycellulose, 130*
- Atheromatous coronary disease of early onset and parallel course in twins, 403*
- Atherosclerosis for coronary arteries, predilection of, 805*
- Atmosphere, comfortable, rates of water and heat loss from respiratory tract of patients with congestive heart failure who were from subtropical climate and resting in (Burch), 88
- Atmospheric temperature and humidity, influence of variations in, on rates of water and heat loss from respiratory tract of patients with congestive heart failure living in subtropical climate (Burch), 190
- Auricular and ventricular cavities, right, in man, potential variations of (Hecht), 39
 - diastolic murmur with heart block in elderly patients (Rytand), 579
 - fibrillation in association with congestive failure, quinidine in treatment of, 131*
 - flutter, established, combined use of lanatoside C and quinidine sulfate in abolition of (Tandowsky et al.), 617
 - intercurrent, complete auriculoventricular block and bundle branch block with (de Moura), 794
 - size, left, quantitative roentgenographic method for determination of, 405*
 - standstill, 128*
- Auriculoventricular block, complete, and bundle branch block with intercurrent auricular flutter (de Moura), 794
- Auscultation, cardio-esophageal, 267*

B

- Bacterial endarteritis, acute, 673*
- endocarditis, subacute, penicillin in: report to Medical Research Council of 147 patients treated in fourteen centers appointed by Penicillin Clinical Trials Committee, 540*
 - refractory case of, due to *Veillonella gazogenes* clinically arrested by combination of penicillin, sodium para-aminohippurate, and heparin (Loewe et al.), 327
 - results in treatment of, 539*
 - treatment of, with penicillin, 130*
- Behavior of heart during manipulation, indications for removal of intracardiac foreign bodies and (III); foreign bodies in and in relation to thoracic blood vessels and heart (Harken and Zoll), 1
- Beriberi heart disease, 542*
- Bicuspid aortic valve diagnosed during life, 401*
- Bilateral pulmonary infarction and pneumothorax complicating hypertensive, coronary heart disease with myocardial infarction (Rogers), 519
- Bilocular, cor (Bembenista), 394
- Biochemical changes, abnormal, in patients with severe, acute medical illnesses, with and without peripheral vascular failure: medical shock, 132*
- Blood cells, human, powdered, clinical evaluation of, in treatment of ulcers of extremities associated with vascular disorders (Anderson et al.), 754
- flow, peripheral, rectal and skin temperature in congestive heart failure: effects of rapid digitalization in this state, 811*
 - pulmonary, studies of roentgen density of lungs in humans as measure of, 270*
 - renal, decreased, edema and, in patients with chronic congestive heart failure: evidence of "forward failure" as primary cause of edema, 674*
 - velocity of, in normal pregnant women (Manchester and Loube), 215
- plasma proteins in patients with heart failure, 539*
- pressure, in pulmonary artery, method for determining, 671*
- influence of age on (Russek et al.), 468
- of hypertensive patients, effect of lowering, by high spinal anesthesia on renal function as measured by inulin and diodrast clearance (VI); studies on hypertension, 408*
- residual, of heart, relation between circulation time and amount of (Gernandt and Nylin), 411
- vessels, coronary, in man, attempt at roentgenologic visualization of, 812*

Blood vessels—Cont'd

- thoracic, and heart, foreign bodies in and in relation to; III. Indications for removal of intracardiac foreign bodies and behavior of heart during manipulation (Harken and Zoll), 1
- volume, cardiac "competence," and exercise, central venous pressure in relation to, 812*
- in clinical shock; II. Extent and cause of blood volume reduction in traumatic hemorrhagic and burn shock, 271*

Book reviews, 275, 409, 676, 813

Bundle branch block, complete auriculoventricular block and, with intercurrent auricular flutter (de Moura), 794

C

- Calcium, magnesium and, influence of, on proprioceptive regulation of arterial pressure, 675*
- Capacity, functional, of heart, practical test for determination of, 402*
- Capillary fragility, increased, new drug for treatment of: rutin, 274*
- Carcinoma of esophagus, genesis of aortic perforation secondary to, 674*
- Cardiac arrest after spinal anesthesia; report of case with recovery, 404*
- "competence," blood volume, and exercise, central venous pressure in relation to, 812*
- enlargement in fever therapy induced by intravenous injection of typhoid vaccine, 271*
- dyspnea, abnormalities of respiratory pattern in patients with (Heyer), 457
- failure, some observations on pathogenesis of edema in (Reichsman and Grant), 438
- output in heart failure (Suárez et al.), 339
- size of children with rheumatic heart disease, method for measuring (comparison with cardiothoracic index): angles of clearance, 540*
- vector, construction of (Hill), 72
- weight, significance of, in rats with experimental hypertension, 272*
- Cardio-esophageal auscultation, 267*
- Cardiodynamometry: practical test for determination of functional capacity of heart, 402*
- Cardiopathies, congenital, new classification of, 801*
- Cardiovascular defects in Selective Service registrants (Eanes et al.), 504
 - rejection rates of Selective Service registrants for (Eanes et al.), 506
 - specific diagnostic groups of, in Selective Service registrants (Eanes et al.), 507
 - rejectees, occupations of, in Selective Service registrants (Eanes et al.), 511

Cardiovascular—Cont'd

- rejections in relation to age in Selective Service registrants (Eanes et al.), 510
- renal disease, its prognostic significance in relation to hypertension and: overweight, 804*
- responses to breathing of 100 per cent oxygen at normal barometric pressure, 272*
- syphilis and varicose veins in Selective Service registrants (Eanes et al.), 510
- system in anemia, with note on particular abnormality of sickle cell anemia, 273*
- Cardite reumatica, infeccao reumatica e, 275 (B. Rev.)
- Carotid sinus reflex, hyperactive cardioinhibitory, 543*
- Catheterization, right heart, demonstration of ventricular septal defect by means of (Baldwin et al.), 152
- Cavities, right auricular and ventricular, in man, potential variations of (Hecht), 39
- Children, coronary occlusive disease in infants and, 273*
- Cineroentgenography and electrocardiography, movements of mitro-aortic ring recorded simultaneously by, 270*
- Circulation time and amount of residual blood of heart, relation between (Germandt and Nylin), 411
 - arm-to-tongue, parenteral vitamin B as agent for determining; Part I (Swenson), 612
 - from pulmonary to systemic capillaries, objective method for determining, by use of oximeter, 675*
- Claudication, intermittent, and vascular spasm; I. Is vascular spasm contributory cause of intermittent claudication in patients with structural disease of arteries? 670*
- Clearance, angles of: method for measuring cardiac size of children with rheumatic heart disease (comparison with cardiothoracic index), 540*
- Climate, subtropical, rates of water and heat loss from respiratory tract of patients with congestive heart failure who were from and resting in comfortable atmosphere (Burch), 88
- Clubbed fingers, 268*
- Coagulation of blood, effect of methylxanthines on prothrombin time and, 802*
- Coarctation, atypical, right-sided aorta with, involving only left subclavian artery; hypertension (Master), 778
 - of aorta, roentgenological picture of, and its anatomical basis, 127*
- Coma, fainting and, caused by oxygen lack, circulatory changes during, 539*
- Congenital cardiopathies, new classification of, 801*

- Congestive failure, quinidine in treatment of auricular fibrillation in association with, 131*
 heart failure, influence of variations in atmospheric temperature and humidity on rates of water and heat loss from respiratory tract of patients with, living in subtropical climate (Burch), 190
 rates of water and heat loss from respiratory tract of patients with, who were from subtropical climate and resting in comfortable atmosphere (Burch), 88
 Cor adiposum: heart block caused by fat infiltration of interventricular septum (Spain and Cathcart), 659
 biloculare (Bembenista), 394
 pulmonale, chronic, study of, 804*
 Cornell conferences on therapy, 275 (B. Rev.)
 Coronary arteries, predilection of atherosclerosis for, 805*
 artery, left, anomalous origin of, from pulmonary artery; report of case diagnosed clinically and confirmed by necropsy (Eidlow and Mackenzie), 243
 occlusion, acute pericarditis simulating (Coffen and Searf), 515
 ostial stenosis and myocardial infarction, syphilitic gummatous aortitis as cause of (Weinberg and Beissinger), 665
 circulation, 269*
 disease, anoxemia and exercise tests in diagnosis of (Björck), 689
 atheromatous, of early onset and parallel course in twins, 403*
 heart disease, hypertensive, with myocardial infarction, bilateral pulmonary infarction and pneumothorax complicating (Rogers), 519
 occlusion in Negroes, 400*
 progressive, with associated mediastinal tumor, pain of unusual duration due to (Donovan), 786
 occlusive disease in infants and children, 273*
 sinus rhythm (Scherf and Harris), 443
 thrombosis with myocardial infarction, experiences with dicumarol (3,3'-methylene-bis-[4-hydroxy coumarin]) in treatment of (Wright), 20
 Cutaneous diphtheria, combined sulfonamide and diphtheritic myocarditis in (Greene), 250
 Cyanosis, experimental, and anoxemia, effects of artificial ductus arteriosus on, 407*
 Defect, ventricular septal, demonstration of, by means of right heart catheterization (Baldwin et al.), 152
 Defects, cardiovascular, in Selective Service registrants (Eanes et al.), 504
 Diabetes mellitus, relation of tobacco smoking to arteriosclerosis obliterans in, 400*
 Diastolic murmur, auricular, with heart block in elderly patients (Rytand), 579
 Dicumarol (3,3'-methylene-bis-[4-hydroxy coumarin]), experiences with, in the treatment of coronary thrombosis with myocardial infarction (Wright), 20
 use of, diagnostic and therapeutic indications; serial prothrombin estimations in cardiac patients, 268*
 Digitalization, rapid, effects of, in this state: peripheral blood flow, rectal and skin temperature in congestive heart failure, 811*
 Diodrast clearance, inulin and, effect of lowering blood pressures of hypertensive patients by high spinal anesthesia on renal function as measured by (V1); studies on hypertension, 408*
 Diphtheria, cutaneous, combined sulfonamide and diphtheritic myocarditis in (Greene), 250
 Diphtheritic myocarditis, combined sulfonamide and, in cutaneous diphtheria (Greene), 250
 Dorsalis pedis, palpable, and posterior tibial pulsations, incidence of, in soldiers (Silverman), 82
 Ductus arteriosus, artificial, effects of, on experimental cyanosis and anoxemia, 407*
 Dyspnea, cardiac, abnormalities of respiratory pattern in patients with (Hoyer), 457
- ## E
- Edema and decreased renal blood flow in patients with chronic congestive heart failure: evidence of "forward failure" as primary cause of edema, 674*
 in cardiac failure, some observations on pathogenesis of (Reichsman and Grant), 438
 Einthoven's triangle (Wilson et al.), 277
 theory of unipolar electrocardiographic leads, and interpretation of precordial electrocardiogram (Wilson et al.), 277
 Electrical currents, some results of recording, from right auricle and ventricle by direct intracavity lead, 401*
 Electrocardiogram, esophageal, in arrhythmias and tachycardias (Butterworth and Poindexter), 681
 in hypoxic state, newer investigations on, 809*

- Electrocardiogram—Cont'd
 in normal subjects, effect of meals on (Simonson et al.), 202
 in toxemias of pregnancy, 673*
 normal and pathological P-Q time of, 127*
 precordial, in high lateral myocardial infarction (Rosenbaum et al.), 135
 interpretation of (Wilson et al.), 293
 on Einthoven's triangle, theory of unipolar electrocardiographic leads, and interpretation of (Wilson et al.), 277
 T wave of, at different age levels (Suárez and Suárez, Jr.), 480
- Electrocardiograms, multiple precordial, simplified and more standardized technique for recording (Geiger and Goerner), 163
- Electrocardiographic changes occurring during treatment with fuadin solution (Beaser and Rodriguez-Molina), 634
 during upper respiratory infections (Young), 383
 findings, clinical analysis of primary atypical pneumonia, with discussion of, 542*
 interpretation, 409 (B. Rev.)
 leads, unipolar, theory of, Einthoven's triangle, and interpretation of precordial electrocardiogram (Wilson et al.), 277
 manifestation, unusual, of intra-auricular dissociation in pair of identical twins, 128*
 patterns in penetrating wounds of heart (Noth), 713
 survey on three hundred Negro and two hundred white subjects, persistence of juvenile pattern in precordial leads of healthy adult Negroes, with report of (Littmann), 370
 syndrome, paroxysmal ventricular tachycardia followed by (Smith), 257
- Electrocardiography, 409 (B. Rev.)
 following exercise, peculiar conduction disturbance persisting latently after recovery from complete heart block and disclosed only by, 128*
 in practice, 676 (B. Rev.)
 movements of mitro-aortic ring recorded simultaneously by cinerentgenography and, 270*
- Elektrokardiogramm, Beitrag zur Beurteilung des runden Überganges von R und ST Strecke in, 132*
- Elektrokymograph for recording heart motion utilizing the roentgenoscope, 399*
- Elderly patients, auricular diastolic murmur with heart block in (Rytand), 579
- Embolism, thrombosis and, 125*
- Endarteritis, bacterial, acute, 673*
- Endocardial sclerosis in infants and children, 810*
- Endocarditis, bacterial, subacute, complicated by pregnancy, successfully treated with penicillin, 399*
- Endocarditis, bacterial, subacute—Cont'd
 refractory case of, due to *Veillonella gazogenes* clinically arrested by combination of penicillin, sodium para-aminohippurate, and heparin (Loewe et al.), 327
 results in treatment of, 539*
 treatment of, with penicillin, 130*
 meningococcus, 274*
- Epidemiological and sociological observations, some, incidence of rheumatic fever and heart disease in school children in Dublin, Georgia, with (Quinn), 234
- Esophageal electrocardiogram in arrhythmias and tachycardias (Butterworth and Poindexter), 681
- Essential hypertension; renin in (Taquini and Fasciolo), 357
- Esters, synthetic, of strophanthidin, acetate, propionate, butyrate, and benzoate, behavior of, in man, 126*
- Exercise, cardiac "competence," blood volume, and, central venous pressure in relation to, 812*
 tests, anoxemia and, in diagnosis of coronary disease (Börck), 689
- Extremities, ulcers of, associated with vascular disorders, clinical evaluation of powdered human blood cells in treatment of (Anderson et al), 754
 upper, neurovascular syndrome as manifested in (Paull), 32
- Extremity, lower, varicosities of, 810*

F

- Failure, cardiac, some observations on pathogenesis of edema in (Reichsman and Grant), 438
 heart, cardiac output in (Suárez et al.), 339
- Fainting and coma caused by oxygen lack, circulatory changes during, 539*
- Fat infiltration of interventricular septum (cor adiposum), heart block caused by (Spain and Cathcart), 659
- Fever, rheumatic, acute, effect of salicylate on (Warren et al.), 311
 and heart disease, incidence of, in school children in Dublin, Georgia, with some epidemiological and sociological observations (Quinn), 234
 therapy induced by intravenous injection of typhoid vaccine, cardiac enlargement in, 271*
- Fibrillation, transient ventricular (Zimdahl and Fulton), 117
- Fingers, clubbed, 268*
- Flutter, auricular, established, combined use of lanatoside C and quinidine sulfate in abolition of (Tandowsky et al.), 617
 intercurrent, complete auriculoventricular block and bundle branch block with (de Moura), 794

Foreign bodies in and in relation to thoracic blood vessels and heart; III. Indications for removal of intracardiac foreign bodies and behavior of heart during manipulation (Harken and Zoll), 1

Fuadin solution, electrocardiographic changes occurring during treatment with (Beaser and Rodriguez-Molina), 634

G

Gaskell effect, study of, 673*

Gastrointestinal tract, syndrome of abdominal aortic aneurysm rupturing into (Hunt and Weller), 571

Gazogenes, *Veillonella*, refractory case of subacute bacterial endocarditis due to, clinically arrested by combination of penicillin, sodium para-aminohippurate, and heparin (Loewe et al.), 327

Georgia, Dublin, incidence of rheumatic fever and heart disease in school children in, with some epidemiological and sociological observations (Quinn), 234

Glomerulonephritis, acute, purpuric manifestations of rheumatic fever and (Jones and Moore), 529

Gummatous aortitis, syphilitic, as cause of coronary artery ostial stenosis and myocardial infarction (Weinberg and Beissinger), 665

H

Heart block, auricular diastolic murmur with, in elderly patients (Rytand), 579
caused by fat infiltration of interventricular septum (cor adiposum) (Spain and Cathcart), 659

complete, peculiar conduction disturbance persisting latently after recovery from, and disclosed only by electrocardiography following exercise, 128*

disease, beriberi, 542*

coronary, hypertensive, with myocardial infarction, bilateral pulmonary infarction and pneumothorax complicating (Rogers), 519

incidence of rheumatic fever and, in school children in Dublin, Georgia, with some epidemiological and sociological observations (Quinn), 234

rheumatic, gross vascularity of mitral valve as stigma of, 131*

rheumatic fever and, in North African and Mediterranean Theater of Operations, United States Army (Bland), 545

valvular, effect of salicylate on (Warren et al.), 320

electrocardiographic patterns in penetrating wounds of (Noth), 713

Heart—Cont'd

failure, blood plasma proteins in patients with, 539*

cardiac output in (Suárez et al.), 339

congestive, influence of variations in atmospheric temperature and humidity on rates of water and heat loss from respiratory tract of patients with, living in subtropical climate (Burch), 190

low-sodium diet and free fluid intake in treatment of, 404*

peripheral blood flow, rectal and skin temperature in: effects of rapid digitalization in this state, 811*

proteinuria of effort and its significance in diagnosis of, 862*

rates of water and heat loss from respiratory tract of patients with, who were from subtropical climate and resting in comfortable atmosphere (Burch), 88

fluids in, 803*

foreign bodies in and in relation to thoracic blood vessels and; III. Indications for removal of intracardiac foreign bodies and behavior of heart during manipulation (Harken and Zoll), 1

functional capacity of, practical test for determination of, 402*

hypertrophy of, of unknown etiology in young adults: report of four cases with autopsies (Norris and Pote), 599

in primary systemic amyloidosis (Lindsay), 419

motion, electrokymograph for recording, utilizing roentgenoscope, 399*

relation between circulation time and amount of residual blood of (Gernandt and Nylin), 411

right, catheterization, demonstration of ventricular septal defect by means of (Baldwin et al.), 152

stimulating action of acetylcholine on, 418*
weight; II. Effect of tuberculosis on heart weight, 674*

Heat loss, water and, from respiratory tract of patients with congestive heart failure living in subtropical climate, influence of variations in atmospheric temperature and humidity on (Burch), 190

water and, loss, rates of, from respiratory tract of patients with congestive heart failure who were from subtropical climate and resting in comfortable atmosphere (Burch), 88

Heparin, penicillin, sodium para-aminohippurate, and, refractory case of subacute bacterial endocarditis due to *Veillonella gazogenes* clinically arrested by combination of (Loewe et al.), 327

therapy in acute venous thrombosis, 406*

- Human blood cells, powdered, clinical evaluation of, in treatment of ulcers of extremities associated with vascular disorders (Anderson et al.), 754
- Humidity, influence of variations in atmospheric temperature and, on rates of water and heat loss from respiratory tract of patients with congestive heart failure living in subtropical climate (Burch), 190
- Hydroxycellulose, atheromatosis in dogs following repeated intravenous injections of, 130*
- Hypertension and cardiovascular renal disease, its prognostic significance in relation to: overweight, 804*
arterial, relation of arterial pulse pressure to arteriovenous oxygen difference, especially in, 126*
selection of patients with, for treatment by repeated injections of pitressin, 806*
essential, analysis of surgical failures and fatalities following thoracolumbar sympathectomy for, 805*
renin in (Taquini and Fasciolo), 357
splenorenopexy in, 407*
experimental, significance of cardiac weight in rats with, 272*
right-sided aorta with atypical coarctation involving only left subclavian artery (Master), 778
some effects of rice diet treatment of kidney disease and, 808*
studies on; VI. Effect of lowering blood pressures of hypertensive patients by high spinal anesthesia on renal function as measured by inulin and diodrast clearance, 408*
unilateral renal, present status of, 130*
- Hypertensive, coronary heart disease with myocardial infarction, bilateral pulmonary infarction and pneumothorax complicating (Rogers), 519
patient, selection of, for sympathectomy, 267*
- Hypertrophy of heart of unknown etiology in young adults: report of four cases with autopsies (Norris and Pote), 599
- Hypothyroidism and mild myxedema from thiocyanate intoxication, 811*
- Hypoxemic state, newer investigations on electrodiagram in, 809*
- I
- Iliac veins, ligation of inferior vena cava or; report of 136 operations, 807*
- Infant, paroxysmal nodal tachycardia in, 808*
- Infants and children, coronary occlusive disease in, 273*
- Infarction, high lateral myocardial, precordial electrocardiogram in (Rosenbaum et al.), 135
- Infarction—Cont'd
myocardial, bilateral pulmonary infarction and pneumothorax complicating hypertensive, coronary heart disease with (Rogers), 519
experiences with dicumarol (3,3' methylene-bis-[4-hydroxycoumarin]) in treatment of coronary thrombosis with (Wright), 20
syphilitic gummatous aortitis as cause of coronary artery ostial stenosis and (Weinberg and Beissinger), 665
pulmonary, bilateral, and pneumothorax complicating hypertensive, coronary heart disease with myocardial infarction (Rogers), 519
- Infeccao reumatica e cardite reumatica, 275 (B. Rev.)
- Infections, respiratory, upper, electrocardiographic changes occurring during (Young), 383
- Inflammations, scarifying, calcifying, of pericardial sac, and results of operative management, on, 809*
- Ingestion of large amounts of sodium chloride, effects of, on arterial and venous pressures of normal subjects (Grant and Reichsman), 704
- Innervation of veins; its role in pain, venospasm, and collateral circulation, 671*
- Insufficiency, tricuspid, parasternal leads in (Ellis and Brown), 364
- Interventricular septum (cor adiposum), heart block caused by fat infiltration of (Spain and Cathcart), 659
- Intra-auricular dissociation in pair of identical twins, unusual electrocardiographic manifestation of, 128*
- Intracardiac foreign bodies, indications for removal of, and behavior of heart during manipulation (III); foreign bodies in and in relation to thoracic blood vessels and heart (Harken and Zoll), 1
- Inulin and diodrast clearance, effect of lowering blood pressures of hypertensive patients by high spinal anesthesia on renal function as measured by (VI); studies on hypertension, 408*
- J
- Juvenile pattern, persistence of, in precordial leads of healthy adult Negroes, with report of electrocardiographic survey on three hundred Negro and two hundred white subjects (Littmann), 370
- K
- Kidney disease and hypertension, some effects of rice diet treatment of, 808*

L

- Lanatoside C and quinidine sulfate, combined use of, in abolition of established auricular flutter (Tandowsky et al.), 617
- Lead, intracavity direct, some results of recording electrical currents from right auricle and ventricle by, 401*
- Leads, electrocardiographic, unipolar, theory of, Einthoven's triangle, and interpretation of precordial electrocardiogram (Wilson et al.), 277
- para-sternal, in tricuspid insufficiency (Ellis and Brown), 364
- precordial, of healthy adult Negroes, persistence of juvenile pattern in, with report of electrocardiographic survey on three hundred Negro and two hundred white subjects (Littmann), 370
- Left coronary artery, anomalous origin of, from pulmonary artery; report of case diagnosed clinically and confirmed by necropsy (Eidlow and Mackenzie), 243

Letters, 397

Life expectancy in angina pectoris, 269*

Lumbar sympathectomy for chronic leg ulcers, 405*

Lupus erythematosus disseminatus and related diseases, pathogenetic studies on, 126*

Lymphedema of arm, post-operative, prevention and treatment of, 672*

M

Magnesium and calcium, influence of, on proprioceptive regulation of arterial pressure, 675*

Manipulation, indications for removal of intracardiac foreign bodies and behavior of heart during (III); foreign bodies in and in relation to thoracic blood vessels and heart (Harken and Zoll), 1

Meals, effect of, on electrocardiogram in normal subjects (Simonson et al.), 202

Mediastinal tumor, associated, pain of unusual duration due to progressive coronary occlusion with (Donovan), 786

Medical and surgical treatment of trench foot (Abramson et al.), 61

shock; abnormal biochemical changes in patients with severe, acute medical illnesses, with and without peripheral vascular failure, 132*

Mediterranean, North African and, Theater of Operations, United States Army, rheumatic fever and rheumatic heart disease in (Bland), 545

Meiosis, subacute endocarditis, 271*

3,3'-Methylene-bis-(4-hydroxycoumarin), experiences with, in treatment of coronary thrombosis with myocardial infarction (Wright), 20

Methylxanthines, effect of, on prothrombin time and coagulation of blood, 802*

Mitral valve, gross vascularity of, as stigma of rheumatic heart disease, 131*

Mitro-aortic ring, movements of, recorded simultaneously by cinerentgenography and electrocardiography, 270*

Multiple precordial electrocardiograms, simplified and more standardized technique for recording (Geiger and Goerner), 163

Murmur, diastolic, auricular, with heart block in elderly patients (Rytand), 579

Myocardial infarction, bilateral pulmonary infarction and pneumothorax complicating hypertensive, coronary heart disease with (Rogers), 519

experiences with dicumarol (3,3'-methylene-bis-[4-hydroxycoumarin]) in treatment of coronary thrombosis with (Wright), 20

high lateral, precordial electrocardiogram in (Rosenbaum et al.), 135

syphilitic gummatous aortitis as cause of coronary artery ostial stenosis and (Weinberg and Beissinger), 665

Myocardii, amyloidosis, 127*

Myocarditis, combined sulfonamide and diphtheritic, in cutaneous diphtheria (Greene), 250

Myxedema, mild, hypothyroidism and, from thiocyanate intoxication, 811*

N

Negroes, adult, healthy, persistence of juvenile pattern in precordial leads of, with report of electrocardiographic survey on three hundred Negro and two hundred white subjects (Littmann), 370

coronary occlusion in, 400*

Neurocirculatory asthenia, effect of exercise on soldiers with, 671*

syndrome (neurocirculatory asthenia), in soldiers, 126*

Neurovascular syndrome as manifested in upper extremities (Paull), 32

Newborn, rubella in pregnancy causing malformations in, 131*

Noctal tachycardia, paroxysmal, plasma concentrations of quinidine with particular reference to therapeutically effective levels in two cases of (Delevett and Poindexter), 697

Normal pregnant women, velocity of blood flow in (Manchester and Loubé), 215

subjects, effect of meals on electrocardiogram in (Simonson et al.), 202

Normal subjects—Cont'd

effects of ingestion of large amounts of sodium chloride on arterial and venous pressures of (Grant and Reichsman), 704

North African and Mediterranean Theater of Operations, United States Army. rheumatic fever and rheumatic heart disease in (Bland), 545

O

Obliteration, venous, collateral channels in, 807*

Occlusion, coronary artery, acute pericarditis simulating (Coffen and Scarf), 515
progressive, with associated mediastinal tumor, pain of unusual duration, due to (Donovan), 786

Orthostatic paroxysmal ventricular tachycardia (Peters and Penner), 645

Ostial stenosis, coronary artery, and myocardial infarction, syphilitic gummatous aortitis as cause of (Weinberg and Beissinger), 665

Output, cardiac, in heart failure (Suárez et al.), 339

Overweight: its prognostic significance in relation to hypertension and cardiovascular renal disease, 804*

Oximeter, objective method for determining circulation time from pulmonary to systemic capillaries by use of, 675*

Oxygen difference, arteriovenous, relation of arterial pulse pressure to, especially in arterial hypertension, 126*

100 per cent, cardiovascular responses to breathing of, at normal barometric pressure, 272*

P

Pain of unusual duration due to progressive coronary occlusion with associated mediastinal tumor (Donovan), 786

Palpable dorsalis pedis and posterior tibial pulsations, incidence of, in soldiers (Silverman), 82

Para-aminohippurate, sodium, penicillin, and heparin, refractory case of subacute bacterial endocarditis due to *Veillonella gazogenes* clinically arrested by combination of (Loewe et al.), 327

Parasternal leads in tricuspid insufficiency (Ellis and Brown), 364

Parenteral vitamin B as agent for determining arm-to-tongue circulation time; Part I (Swenson), 612

Paroxysmal nodal tachycardia, plasma concentrations of quinidine with particular reference to therapeutically effective levels in two cases of (Delevett and Poindexter), 697

Paroxysmal—Cont'd

ventricular tachycardia followed by electrocardiographic syndrome (Smith), 257

orthostatic (Peters and Penner), 645

Pathogenesis of edema in cardiac failure, some observations on (Reichsman and Grant), 438

Patterns, electrocardiographic, in penetrating wounds of heart (Noth), 713

Pedis, palpable dorsalis, and posterior tibial pulsations, incidence of, in soldiers (Silverman), 82

Penicillin in subacute bacterial endocarditis: report to Medical Research Council of 147 patients treated in fourteen centers appointed by Penicillin Clinical Trials Committee, 540*

observations of treatment of scarlet fever with, 132*

sodium para-aminohippurate, and heparin, refractory case of subacute bacterial endocarditis due to *Veillonella gazogenes* clinically arrested by combination of (Loewe et al.), 327

subacute bacterial endocarditis complicated by pregnancy, successfully treated with, 399*

treatment of bacterial endocarditis with, 130*

Pericardial sac, on calcifying, scarifying inflammations of, and results of operative management, 809*

Pericarditis, acute, in young adults (Nay and Boyer), 222

simulating coronary artery occlusion (Coffen and Scarf), 515

Peripheral arterial diseases, 125*

Phonocardiographic, auscultation collective (acoustique—technique—clinique), 676 (B. Rev.)

Pitressin, selection of patients with arterial hypertension for treatment by repeated injections of, 806*

Plasma concentrations of quinidine with particular reference to therapeutically effective levels in two cases of paroxysmal nodal tachycardia (Delevett and Poindexter), 697

Pneumonia, atypical, primary, clinical analysis of, with discussion of electrocardiographic findings, 542*

Pneumonitis, non-suppurative post-streptococcic (rheumatic), 541*
occurring in rheumatic fever, 807*

Pneumothorax, bilateral pulmonary infarction and, complicating hypertensive, coronary heart disease with myocardial infarction (Rogers), 519

Posterior tibial pulsations, incidence of palpable dorsalis pedis and, in soldiers (Silverman), 82

- Potential variations of right auricular and ventricular cavities in man (Hecht), 39
- P-Q time, normal and pathological, of electrocardiogram, 127*
- Precordial electrocardiogram in high lateral myocardial infarction (Rosenbaum et al.), 135
- interpretation of (Wilson et al.), 293
- on Einthoven's triangle, theory of unipolar electrocardiographic leads and interpretation of (Wilson et al.), 277
- T wave of, at different age levels (Suárez and Suárez, Jr.), 480
- electrocardiograms, multiple, simplified and more standardized technique for recording (Geiger and Goerner), 163
- leads of healthy adult Negroes, persistence of juvenile pattern in, with report of electrocardiographic survey on three hundred Negro and two hundred white subjects (Littmann), 370
- Pregnancy, electrocardiogram in toxemias of, 673*
- rubella in, causing malformations in newborn, 131*
- subacute bacterial endocarditis complicated by, successfully treated with penicillin, 399*
- women, normal, velocity of blood flow in (Manchester and Louhe), 215
- Pressure, intravascular and extravascular, in Valsalva's experiment, 801*
- Pressures, arterial and venous, of normal subjects, effects of ingestion of large amounts of sodium chloride on (Grant and Reichsman), 704
- Procaine, intravenous, treatment of acute arrhythmias during anesthesia by, 270*
- Proteinuria of effort and its significance in diagnosis of congestive heart failure, 802*
- Prothrombin estimations, serial, in cardiac patients; diagnostic and therapeutic indications, use of dicumarol, 268*
- time and coagulation of blood, effect of methylxanthines on, 802*
- Pulmonary artery, anomalous origin of left coronary artery from; report of case diagnosed clinically and confirmed by necropsy (Eidlow and Mackenzie), 243
- method for determining blood pressure in, 671*
- thromboangiitis of pulmonary vessels associated with aneurysm of; report of case, 809*
- infarction, bilateral, and pneumothorax complicating hypertensive, coronary heart disease with myocardial infarction (Rogers), 519
- Pulsations, palpable dorsalis pedis and posterior tibial, incidence of, in soldiers (Silverman), 82
- Pulse pressure, arterial, relation of, to arterio-venous oxygen difference, especially in arterial hypertension, 126*
- Purpuric manifestations of rheumatic fever and acute glomerulonephritis (Jones and Moore), 529
- ### Q
- QRS complex configurations in Wolff-Parkinson-White syndrome, notes on similarity of (Burch and Kimball), 560
- Quinidine in treatment of auricular fibrillation in association with congestive failure, 131*
- plasma concentrations of, with particular reference to therapeutically effective levels in two cases of paroxysmal nodal tachycardia (Delevett and Poindexter), 697
- sulfate, combined use of lanatoside C and, in abolition of established auricular flutter (Tandowsky et al.), 617
- ### R
- R und ST Strecke in Elektrokardiogrammen: Beitrag zur Interpretation der Rhythmusstörungen von, 132*
- Reconditioning program for patients with trench foot (Abramson et al.), 67
- Recording multiple precordial electrocardiograms, simplified and more standardized technique for (Geiger and Goerner), 163
- Renal hypertension, unilateral, present status of, 130*
- Renin in essential hypertension (Taquini and Fasciolo), 357
- Residual blood of heart, relation between circulation time and amount of (Gernandt and Nylin), 411
- Respiratory infections, upper, electrocardiographic changes occurring during (Young), 383
- pattern, abnormalities of, in patients with cardiac dyspnea (Heyer), 457
- tract of patients with congestive heart failure living in subtropical climate, influence of variations in atmospheric temperature and humidity on rates of water and heat loss from (Burch), 190
- of patients with congestive heart failure who were from subtropical climate and resting in comfortable atmosphere, rates of water and heat loss from (Burch), 88
- Rheumatica, cardite, infeccao reumatica e, 275 (B. Rev.)

Rheumatic fever, acute, effect of salicylate on (Warren et al.), 311

- and acute glomerulonephritis, purpuric manifestations of (Jones and Moore), 529
- and heart disease, incidence of, in school children in Dublin, Georgia, with some epidemiological and sociological observations (Quinn), 234
- and rheumatic heart disease in North African and Mediterranean Theater of Operations, United States Army (Bland), 545
- and rheumatoid arthritis, value of Speransky's method of spinal pumping in treatment of, 129*
- in Naval enlisted personnel; III. Physiologic and toxic effects of intensive salicylate therapy in acute cases, 401*
- pneumonitis occurring in, 807*
- treatment of, by roentgen ray irradiation, 670*
- heart disease, gross vascularity of mitral valve as stigma of, 131*
- method for measuring cardiac size of children with (comparison with cardiothoracic index): angles of clearance, 540*
- rheumatic fever and, in North African and Mediterranean Theater of Operations, United States Army (Bland), 545
- pneumonitis, non-suppurative post-streptococcic, 541*

Rheumatoid arthritis, value of Speransky's method of spinal pumping in treatment of rheumatic fever and, 129*

Rhythm, sinus, coronary (Scherf and Harris), 443

Rice diet treatment of kidney disease and hypertension, some effects of, 808*

Right heart catheterization, demonstration of ventricular septal defect by means of (Baldwin et al.), 152

Roentgen density of lungs, study of, in humans as measure of pulmonary blood flow, 270*

- ray irradiation, treatment of rheumatic fever by, 670*

Roentgenographic method, quantitative, for determination of left auricular size, 405*

Roentgenologic visualization of coronary blood vessels in man, an attempt at, 812*

Rubella in pregnancy causing malformations in newborn, 131*

Rupture of aortic valves due to effort, 273*

Rutin: new drug for treatment of increased capillary fragility, 274*

S

Salicylate, effect of, on acute rheumatic fever (Warren et al.), 311

- on fever (Warren et al.), 318
- on pericarditis (Warren et al.), 322
- on polycyclic attacks (Warren et al.), 319
- on P-R interval (Warren et al.), 323
- on sedimentation rate (Warren et al.), 315
- on valvular heart disease (Warren et al.), 320

- therapy, intensive, physiologic and toxic effects of, in acute cases (III); rheumatic fever in Naval enlisted personnel, 401*
- toxicity: probable mechanism of its action, 272*

Saline solution, hypertonic, circulatory changes following injection of; application to study of angina pectoris, 129*

Scarlet fever, observations on treatment of, with penicillin, 132*

School children in Dublin, Georgia, incidence of rheumatic fever and heart disease in, with some epidemiological and sociological observations (Quinn), 234

Sclerosis, endocardial, in infants and children, 810*

- vascular, peripheral, sympathectomy in, 802*

Sedimentation rate, effect of salicylate on (Warren et al.), 315

Selective Service registrants, cardiovascular defects in (Eanes et al.), 504

Septal defect, ventricular, demonstration of, by means of right heart catheterization (Baldwin et al.), 152

Sickle cell anemia, cardiovascular system in anemia, with note on particular abnormality of, 273*

Sinus reflex, carotid, hyperactive cardioinhibitory, 543*

- rhythm, coronary (Scherf and Harris), 443

Shock, clinical, blood volume in; II. Extent and cause of blood volume reduction in traumatic hemorrhagic and burn shock, 271*

- concentrated human albumin in treatment of, 672*
- medical: abnormal biochemical changes in patients with severe, acute medical illnesses, with and without peripheral vascular failure, 132*

Smoking, tobacco, relation of, to arteriosclerosis obliterans in diabetes mellitus, 400*

Sociological observations, some epidemiological and, incidence of rheumatic fever and heart disease in school children in Dublin, Georgia, with (Quinn), 234

- Sodium Chloride, effects of ingestion of large amounts of, on arterial and venous pressures of normal subjects (Grant and Reichsman), 704
- low-, diet and free fluid intake in treatment of congestive heart failure, 404*
- para-aminohippurate, penicillin, and heparin, refractory case of subacute bacterial endocarditis due to *Veillonella gazogenes* clinically arrested by combination of (Loewe et al.), 327
- Soldiers, incidence of palpable dorsalis pedis and posterior tibial pulsations in (Silverman), 82
- Spinal anesthesia, cardiac arrest after; report of case with recovery, 404*
- high, effect of lowering blood pressures of hypertensive patients by, on renal function as measured by inulin and diodrast clearance (VI); studies on hypertension, 408*
- pumping, value of Speransky's method of, in treatment of rheumatic fever and rheumatoid arthritis, 129*
- Splenorenopexy in essential hypertension, 407*
- ST Streeke, Beitrag zur Beurteilung des runden Überganges von R und, in Elektrokardiogramm, 132*
- Stenosis, aortic, due to calcified, syphilitic valvulitis, 403*
- ostial, coronary artery, and myocardial infarction, syphilitic gummatous aortitis as cause of (Weinberg and Beissinger), 665
- Strophanthidin, behavior of synthetic esters of, acetate, propionate, butyrate, and benzoate in man, 126*
- Subclavian artery, left, right-sided aorta with atypical coarctation involving only; hypertension (Master), 778
- Subtropical climate, influence of variations in atmospheric temperature and humidity on rates of water and heat loss from respiratory tract of patients with congestive heart failure living in (Burch), 190
- rates of water and heat loss from respiratory tract of patients with congestive heart failure who were from and resting in comfortable atmosphere (Burch), 88
- Sulfonamide and diphtheritic myocarditis, combined, in cutaneous diphtheria (Greene), 250
- Surgical, medical and, treatment of trench foot (Abramson et al.), 61
- Sympathectomy in peripheral vascular sclerosis, 802*
- lumbar, for chronic leg ulcers, 405*
- resection of hypertensive patients for, 267*
- thoracolumbar, for essential hypertension, analysis of surgical failures and fatalities following, 805*
- Sympathetic blocks, repeated; limitation and value, 407*
- Syndrome, electrocardiographic, paroxysmal ventricular tachycardia followed by (Smith), 257
- neurocirculatory syndrome (neurocirculatory asthenia) in soldiers, 126*
- neurovascular, as manifested in upper extremities (Paull), 32
- of abdominal aortic aneurysm rupturing into gastrointestinal tract (Hunt and Weller), 571
- Wolff-Parkinson-White (Littmann and Tarnower), 100
- notes on similarity of QRS complex configurations in (Burch and Kimball), 560
- Synthetic esters of strophanthidin, acetate, propionate, butyrate, and benzoate, behavior of, in man, 126*
- Syphilitic gummatous aortitis as cause of coronary artery ostial stenosis and myocardial infarction (Weinberg and Beissinger), 665
- Systemic amyloidosis, primary, heart in (Lindsay), 419
- T
- T wave of precordial electrocardiogram at different age levels (Suárez and Suárez, Jr.), 480
- Tachycardia, nodal, paroxysmal, in infant, 808*
- plasma concentrations of quinidine with particular reference to therapeutically effective levels in two cases of (Delevett and Poindexter), 697
- ventricular, paroxysmal, followed by electrocardiographic syndrome (Smith), 257
- orthostatic (Peters and Penner), 645
- Tachycardias, esophageal electrocardiogram in arrhythmias and (Butterworth and Poindexter), 681
- Technique, simplified and more standardized, for recording multiple precordial electrocardiograms (Geiger and Goerner), 163
- Temperature, atmospheric, and humidity, influence of variations in, on rates of water and heat loss from respiratory tract of patients with congestive heart failure living in subtropical climate (Burch), 190
- rectal and skin, peripheral blood flow, in congestive heart failure: effects of rapid digitalization in this state, 811*
- Temporal arteritis: generalized vascular disease, 406*
- Testosterone in angina pectoris, 806*
- Therapy, Cornell conferences on, 275 (B. Rev.)
- Thiocyanate intoxication, hypothyroidism and mild myxedema from, 811*

- Thiouracil treatment of angina pectoris, disadvantages of (DiPalma and Ma-Govern), 494
- Thoracic aorta, descending, aneurysm of (Loewenberg and Baer), 653
- blood vessels and heart, foreign bodies in and in relation to; III. Indications for removal of intracardiac foreign bodies and behavior of heart during manipulation (Harken and Zoll), 1
- Thoracolumbar sympathectomy for essential hypertension, analysis of surgical failures and fatalities following, 805*
- Thromboangiitis of pulmonary vessels associated with aneurysm of pulmonary artery: report of case, 809*
- Thrombosis and embolism, 125*
- coronary, with myocardial infarction, experiences with dicumarol (3,3'-methylene-bis-[4-hydroxycoumarin]) in treatment of (Wright), 20
- slowly progressive occlusive, of abdominal portion of aorta, 127*
- venous, acute, heparin therapy in, 400*
- Tibial pulsations, posterior, incidence of palpable dorsalis pedis and, in soldiers (Silverman), 82
- Time, circulation, and amount of residual blood of heart, relation between (Gernandt and Nylin), 411
- Toxicity, salicylate: probable mechanism of its action, 272*
- Tract, respiratory, of patients with congestive heart failure living in subtropical climate, influence of variations in atmospheric temperature and humidity on rates of water and heat loss from (Burch), 190
- Transient ventricular fibrillation (Zimdahl and Fulton), 117
- Traumatic aneurysms of extremities, 407*
- Treatment, thiouracil, of angina pectoris, disadvantages of (DiPalma and Ma-Govern), 494
- Trench foot, clinical picture and treatment of later stage of (Abramson et al.), 52
- Tricuspid insufficiency, parasternal leads in (Ellis and Brown), 364
- Tuberculosis, effect of, on heart weight (II); heart weight, 674*
- Tumor, mediastinal, associated, pain of unusual duration due to progressive coronary occlusion with (Donovan), 786
- Typhoid vaccine, cardiac enlargement in fever therapy induced by intravenous injection of, 271*

U

- Ulcers, leg, chronic, lumbar sympathectomy for, 405*

Ulcers—Cont'd

- of extremities associated with vascular disorders, clinical evaluation of powdered human blood cells in treatment of (Anderson et al.), 754
- Unilateral renal hypertension, present status of, 130*
- Unipolar electrocardiographic leads, theory of, Einthoven's triangle, and interpretation of precordial electrocardiogram (Wilson et al.), 277
- leads (Wilson et al.), 282
- United States Army, rheumatic fever and rheumatic heart disease in North African and Mediterranean Theater of Operations (Bland), 545
- Upper extremities, neurovascular syndrome as manifested in (Paull), 32

V

- Valsalva's experiment, intravascular and extravascular pressure in, 801*
- Valvulitis, syphilitic, calcified, aortic stenosis due to, 403*
- Variations, potential, of right auricular and ventricular cavities in man (Hecht), 39
- Varicose veins, cure of, 125*
- Varicosities of lower extremity, 810*
- Vascular disorders, clinical evaluation of powdered human blood cells in treatment of ulcers of extremities associated with (Anderson et al.), 754
- failure, peripheral, abnormal biochemical changes in patients with severe, acute medical illnesses with and without: medical shock, 132*
- spasm, intermittent claudication and; I. Is vascular spasm contributory cause of intermittent claudication in patients with structural disease of arteries? 670*
- Vascularization of aorta, studies on; I. Vascularization of aorta in normal dog (Schlichter), 770
- Vector cardiac, construction of (Hill), 72
- Veillonella gazogenes*, refractory case of subacute bacterial endocarditis due to, clinically arrested by combination of penicillin, sodium para-aminohippurate, and heparin (Loewe et al.), 327
- Veins, innervation of: its role in pain, venospasm, and collateral circulation, 671*
- varicose, cure of, 125*
- Velocity of blood flow in normal pregnant women (Manchester and Loube), 215
- Vena cava, inferior, or iliac veins, ligation of; report of 136 operations, 807*

Venous, arterial and, pressures of normal subjects, effects of ingestion of large amounts of sodium chloride on (Grant and Reichsman), 704
 obliteration, collateral channels in, 807*
 pressure, clinical studies on; 1. Technique: venous pressure in normal individuals, 804*
 pulse and its graphic recording, 676 (B. Rev.)
 Ventricular aneurysm, longevity with; report of case with survival period of fifteen years, 402*
 cavities, right auricular and, in man, potential variations of (Hecht), 39
 fibrillation, transient (Zindahl and Fulton), 117
 septal defect, demonstration of, by means of right heart catheterization (Baldwin et al.), 152
 tachycardia, paroxysmal, followed by electrocardiographic syndrome (Smith), 257
 orthostatic (Peters and Penner), 645
 Vitamin B, parenteral, as agent for determining arm-to-tongue circulation time; Part I (Swenson), 612

W

Water and heat loss from respiratory tract of patients with congestive heart failure living in subtropical climate, influence of variations in atmospheric temperature and humidity on (Burch), 190

Water and heat loss—Cont'd

rates of, from respiratory tract of patients with congestive heart failure who were from subtropical climate and resting in comfortable atmosphere (Burch), 88

White subjects, two hundred, three hundred Negro and, persistence of juvenile pattern in precordial leads of healthy adult Negroes, with report of electrocardiographic survey on (Littmann), 370

Wolff-Parkinson-White syndrome (Littmann and Tarnower), 100

notes on similarity of QRS complex configurations in (Burch and Kimball), 560

Wounds, penetrating, of heart, electrocardiographic patterns in (Noth), 713

Y

Young adults, hypertrophy of heart of unknown etiology in; report of four cases with autopsies (Norris and Pote), 599

